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(71) Applicant (for all designated States except US): **PHARMACIA & UPJOHN COMPANY** [US/US]; 100 Route
206 North, Peapack, NJ 07977 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **RICHARDS, Ivan**
[US/US]; 3533 E. D Avenue, Kalamazoo, MI 49004
(US). **CAMMARATA, Sue, K.** [US/US]; 10147 Point
O'Woods Drive, Portage, MI 49002 (US). **WEGNER,**

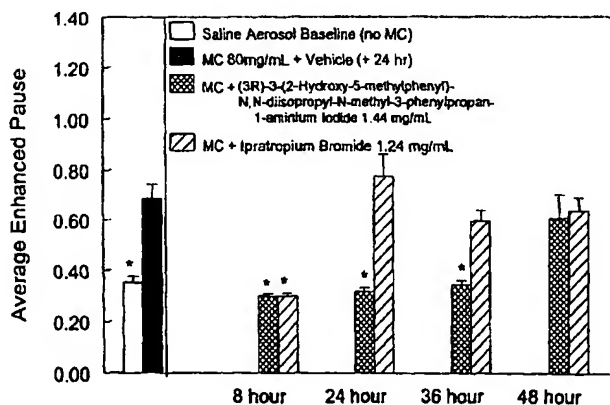
Craig, D. [US/US]; 25850 North Arrowhead Drive,
Mundelein, IL 60060 (US). **HAWLEY, Michael** [US/US];
201 Sunnywood Drive, Kalamazoo, MI 49009 (US).
WARCHOL, Mark, P. [US/US]; 422 Timer Ridge Drive,
Kalamazoo, MI 49006 (US). **KONTNY, Mark** [US/US];
2343 Huntington Lake, Libertyville, IL 60048 (US).
MOROZOWICH, Walter [US/US]; 5330 Chickadee,
Kalamazoo, MI 49002 (US). **KOLBASA, Karen, P.**
[US/US]; 11632 Shaver Road, Schoolcraft, MI 49087
(US). **MOON, Malcolm, W.** [US/US]; 3750 Rosemere
Street, Kalamazoo, MI 49004 (US). **BONAFOUX,**
Dominique [FR/US]; 7337 Pershing, Apartment 1W, St.
Louis, MO 63130 (US). **WOLFSON, Sergey, G.** [US/US];
15599 Hitchcock Road, Chesterfield, MO 63017 (US).
LENNON, Patrick, J. [US/US]; 50 Wilshire Terrace,
Webster Groves, MO 63119 (US).

(74) Agents: **KOZLOWSKI, Holly, D.** et al.; Dinsmore &
Shohl LLP, 1900 Chemed Center, 255 East Fifth Street,
Cincinnati, OH 45202 (US).

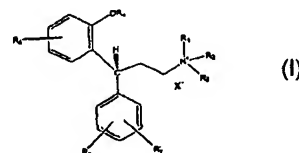
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(54) Title: QUATERNARY AMMONIUM COMPOUNDS AND THEIR USE AS ANTIMUSCARINIC AGENTS



*: p < 0.05 between Vehicle/MC and all other groups



(57) Abstract: Novel quaternary ammonium compounds of the formula (I) and any stereoisomers thereof, wherein, R₁, R₂, and R₃ independently represent C₁-C₆ alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R₁, R₂ and R₃ may form a ring together with the quaternary ammonium nitrogen; R₄ represents -H, -CH₃, or -CO-R₄₋₁, wherein R₄₋₁ represents -(C₁-C₄ alkyl), -(C₁-C₄ alkoxy), or NR₄₋₂R₄₋₃, wherein R₄₋₂ and R₄₋₃ independently represent -H or -(C₁-C₄ alkyl); R₅, R₆ and R₇ independently represent -H, -OCH₃, -OH, -CONH₂, -SO₂NH₂, -F, -Cl, -Br, -I, -CF₃, or -(C₁-C₄ alkyl), optionally substituted with one or two -OH, -(C₁-C₄ alkoxy), -COOH, or -CO-O-(C₁-C₃ alkyl); and X represents an anion of a pharmaceutically acceptable acid, the compounds for use as medicaments, use of the compounds for the manufacture of specific medicaments, and pharmaceutical compositions comprising the compounds. The present invention also concerns a method of treatment involving administration of the compounds.

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QUATERNARY AMMONIUM COMPOUNDS AND THEIR USE AS ANTIMUSCARINIC AGENTS

This application claims the benefit of US Provisional Patent Application No. 60/348 930, filed 26 October 2001, US Provisional Patent Application No. 60/361.979, filed 6 March 2002, and US Provisional Patent Application No. 60/391 521, filed 25 June 2002, and the entire disclosures of which are herein incorporated by reference.

Technical Field

10 The present invention concerns a novel class of quaternary ammonium compounds, pharmaceutical compositions containing the same, the compounds for use as medicaments, and use of the compounds for the manufacture of specific medicaments. The present
15 invention also concerns a method of treatment involving administration of the compounds.

The novel compounds are useful as antimuscarinic agents. In particular, the novel compounds are useful for the treatment of asthma, a group of breathing disorders
20 termed Chronic Obstructive Pulmonary Disease (COPD), allergic rhinitis, and rhinorrhea due to the common cold.

Background of the Invention

US Patent 5,382,600 discloses (substituted) 3,3-diphenylpropylamines useful for treating urinary
25 incontinence. In particular, it discloses 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, with the generic name of tolterodine,
30 as being useful to treat urinary incontinence. Tolterodine is the compound of Example 22 of US 5,382,600.

It is preferred that tolterodine is prepared by the processes of International Publication WO98/29402 (US 5,922,914).

H Postlind et al, Drug Metabolism and Disposition, 26(4): 289-293 (1998) discloses that tolterodine is a muscarinic receptor antagonist. It is presently being sold in a number of different countries for treatment of urinary incontinence under the name Detrol®, marketed by Pharmacia. When tolterodine is used to treat urinary incontinence it is administered perorally as a tablet. The major active metabolite of tolterodine is the 5-hydroxymethyl derivative of tolterodine.

US Patent 5,559,269 and H Postlind et al, Drug Metabolism and Disposition, 26(4): 289-293 (1998) disclose hydroxytolterodine. US Patent 5,559,269 discloses this compound as being useful to treat urinary incontinence. Pharmacol. Toxicol., 81: 169-172 (1997) discloses that hydroxytolterodine has antimuscarinic activity.

The international patent application WO98/43942 discloses therapeutically active diarylpropylamines, which have favorable anticholinergic properties, and which can be used for the treatment of disorders related to urinary incontinence.

WO 02/34245 discloses the use of tolterodine for treating asthma, COPD, and allergic rhinitis.

The currently marketed administration form of tolterodine is film-coated tablets containing 1 mg or 2 mg of tolterodine L-tartrate, or extended release capsules containing 2 mg or 4 mg of tolterodine L-tartrate for release in the gastrointestinal tract. Consumers constantly require alternative delivery forms with favorable efficacy and/or which simplify the treatment, thus improving their quality of life.

Atropine methonitrate and ipratropium are quaternary ammonium derivatives of atropine. Ipratropium bromide is

used by inhalation to produce bronchodilation.

Ipratropium is 8-isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337.

Yono M et al, European Journal of Pharmacology
5 (1999) 368:223-230, is concerned with the pharmacological effects of tolterodine, an antimuscarinic drug, in isolated human urinary bladder smooth muscle.

Ruffmann R et al, The Journal of International
Medical Research (1998) 16:317-330, reviews use of
10 flavoxate hydrochloride or alternative compounds, such as terodiline hydrochloride and emepronium bromide, in the treatment of urge incontinence.

Stewart BH et al, The Journal of Urology (1976)
115:558-559 discloses therapy of mild to moderate stress
15 urinary incontinence with a combination of phenylpropanolamine hydrochloride, chlorpheniramine maleate, and isopropamide iodide in a sustained release capsule.

WO 95/10269 and WO 95/10270 disclose the use of R-
20 and S-terodiline, respectively, as drugs for treating conditions related to the compounds' activities as anticholinergic agents.

Despite the above advances in the art, it is desirable to develop novel pharmaceutical compounds that
25 further improve the quality of life for a large number of individuals.

Summary of the Invention

For these and other purposes, it is an object of the
30 present invention to provide highly efficient pharmaceutical compounds for treatment of asthma.

It is also an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of Chronic Obstructive Pulmonary Disease
35 (COPD).

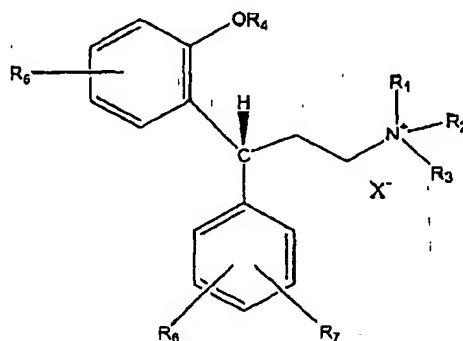
It is a further object of the present invention to provide highly efficient pharmaceutical compounds for treatment of allergic rhinitis.

It is an object of the present invention to provide highly efficient pharmaceutical compounds for treatment of rhinorrhea due to the common cold.

It is also an object of the present invention to provide pharmaceutically effective 3,3-diphenylpropylamine derivatives having an increased residence time in lung upon pulmonary administration.

It is an object of the present invention to provide a novel class of 3,3-diphenylpropylamine derivatives having favorable properties.

For these and other objects that will be evident from the following disclosure, the present invention provides a quaternary ammonium compound of the formula



and any stereoisomers thereof, wherein

R_1 , R_2 and R_3 independently represent C_1 - C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1 , R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen;

R_4 represents

- H,
- CH₃, or
- CO- $R_{4.1}$ wherein $R_{4.1}$ represents
 - (C_1 - C_4 alkyl),
 - (C_1 - C_4 alkoxy), or

5

-NR₄₋₂R₄₋₃, wherein R₄₋₂ and R₄₋₃ independently represent -H or -(C₁-C₄ alkyl), and R₅, R₆ and R₇ independently represent

5 -H,
 -OCH₃,
 -OH,
 -CONH₂,
 -SO₂NH₂,
 -F, -Cl, -Br, -I,
10 -CF₃, or
 -(C₁-C₄ alkyl), optionally substituted with one
or two

 -OH,
 -(C₁-C₄ alkoxy),
15 -COOH, or
 -CO-O-(C₁-C₃ alkyl), and

X⁻ represents an anion of a pharmaceutically acceptable acid.

20 In an embodiment of the compound according to the invention, the carbon stereocenter is (R). In another embodiment of the compound according to the invention, the carbon stereocenter is (S). In yet another embodiment, the compound according to the invention is a mixture of stereoisomers.

25 In a preferred embodiment of the compound according to the invention, at least one of R₁, R₂ and R₃ represents C₁-C₃ alkyl. In a more preferred embodiment, at least one, preferably at least two, of R₁, R₂ and R₃ represents isopropyl. In another more preferred embodiment, at least
30 one of R₁, R₂ and R₃ represents methyl. In yet another more preferred embodiment, at least one of R₁, R₂ and R₃ represents ethyl.

 In one preferred embodiment of the compound according to the invention, R₁ and R₂ jointly form a ring
35 together with the quaternary ammonium nitrogen. In a more

preferred embodiment, said ring comprises from 4 to 6 carbon atoms.

In a preferred embodiment of the compound according to the invention, R_4 represents $-H$, $-CH_3$, or $-CO-R_{4.1}$, wherein $R_{4.1}$ represents C_1 - C_4 alkyl. In a more preferred embodiment, R_4 represents $-H$.

In a preferred embodiment of the compound according to the invention, R_5 represents $-H$, $-Br$, $-Cl$, $-CH_3$, or $-CH_2OH$, more preferably $-CH_3$.

In a preferred embodiment of the compound according to the invention, at least one, more preferably both, of R_6 and R_7 represents $-H$.

In a preferred embodiment of the compound according to the invention, X^- is selected from the group consisting of the anions of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)_n-COOH$ where n is 1 thru 4, $HOOC-CH=CH-COOH$, and benzoic. In a more preferred embodiment, X^- is selected from the group consisting of iodide, bromide, and chloride. In an even more preferred embodiment, X^- represents iodide. In another even more preferred embodiment, X^- represents chloride. In yet another even more preferred embodiment, X^- represents bromide.

More specifically, preferred embodiments of the compound according to the invention include the title compounds of the examples. Particularly preferred embodiments are selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
and

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride.

Moreover, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a quaternary ammonium compound according to the invention, and a suitable pharmaceutical carrier therefor.

The present invention also provides a quaternary ammonium compound according to the invention for use as a medicament.

The present invention provides use of a quaternary ammonium compound according to the invention for the manufacture of a medicament for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder.

Finally, the present invention provides a method of treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to the invention.

Brief Description of the Drawings

Figures 1-3 are diagrams showing average enhanced pause (lung resistance) as a function of time upon inhalation of quaternary ammonium salts according to the invention in Balb/c mice.

Figure 4 is a diagram showing the effects of inhalation of tolterodine and a compound according to the invention, respectively, on the average enhanced pause (lung resistance) as a function of time in Balb/c mice.

Figure 5 is a diagram showing the effects of inhalation of a compound according to the invention and ipratropium bromide, respectively, on the average enhanced pause (lung resistance) as a function of time in Balb/c mice.

Figure 6 is a diagram showing the plasma concentration (pg/ml) of a compound according to the invention with time (hours) following aerosol administration of various amounts in Balb/c mice.

Figure 7 is a diagram showing the plasma concentration (ng/ml) of tolterodine with time (hours) following aerosol administration of various amounts in mice.

10 Description of the Invention

In describing the preferred embodiment, certain terminology will be utilized for the sake of clarity. Such terminology is intended to encompass the recited embodiments, as well as all technical equivalents that
15 operate in a similar manner for a similar purpose to achieve a similar result. To the extent that any pharmaceutically active compound is disclosed or claimed, it is expressly intended to include all active metabolites produced in vivo, and, is expressly intended
20 to include all enantiomers, isomers or tautomers where the compound is capable of being present in its enantiomeric, isomeric or tautomeric form.

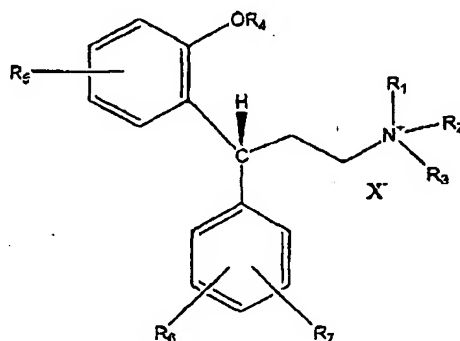
The compounds of the invention can be prepared by
25 one skilled in the art just by knowing the chemical structure of the compound to be prepared. The invention is the compounds themselves, not the process chemistry to make them. The chemistry is known to those skilled in the art.

30 Accordingly, the compounds of the present invention are quaternary ammonium compounds and are prepared by means, well known to those skilled in the art, for preparing quaternary ammonium compounds from tertiary amines, using the tertiary amines of US Patent 5,382,600
35 and other known compounds as starting materials. The general term "quaternary ammonium compound" relates to

any compound that can be regarded as derived from ammonium hydroxide or an ammonium salt by replacement of all four hydrogen atoms of the NH_4^+ -ion by organic groups.

The specific compounds are for nomenclature reasons (see e.g. Chemical Abstracts) named as "aminium" compounds, but it is possible to use the term "ammonium" in the names. For example, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide can also be named as an ammonium compound: (3R)-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]diisopropylmethyllumonium bromide.

More specifically, the invention concerns quaternary ammonium compounds of the formula:



and any stereoisomers thereof, wherein R_1 - R_7 and X^- are as follows.

R_1 , R_2 and R_3 independently represent C_1 - C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and any two of R_1 , R_2 and R_3 may form a ring together with the quaternary ammonium nitrogen.

R_4 represents $-H$, $-CH_3$, or $-CO-R_{4-1}$, wherein R_{4-1} represents $-(C_1-C_4 \text{ alkyl})$, $-(C_1-C_4 \text{ alkoxy})$, or $-NR_{4-2}R_{4-3}$, wherein R_{4-2} and R_{4-3} independently represent $-H$ or $-(C_1-C_4 \text{ alkyl})$.

R_5 , R_6 and R_7 independently represent $-H$, $-OCH_3$, $-OH$, $-CONH_2$ (carbamoyl), $-SO_2NH_2$ (sulphamoyl), $-F$, $-Cl$, $-Br$, $-I$, $-CF_3$, or $-(C_1-C_4 \text{ alkyl})$, optionally substituted with

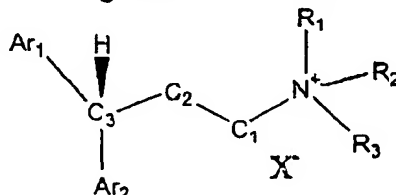
one or two -OH, -(C₁-C₄ alkoxy), -COOH, or -CO-O-(C₁-C₃ alkyl), and X⁻ represents an anion of a pharmaceutically acceptable acid.

5 By way of example, a tertiary amine according to US Patent 5,382,600, or its salt, is dissolved in a suitable solvent. The tertiary amine is allowed to react with an organic substrate, e.g. an organic halide.

The substrate contains a C₁-C₆ alkyl, preferably a
10 C₁-C₃ alkyl, optionally substituted with phenyl, and a leaving group. The identity of the leaving group is not critical, but it is preferred that the leaving group is a halide, such as iodide or bromide. Thus, exemplary
15 substrates include methyl iodide, methyl bromide, ethyl iodide, propyl iodide, benzyl bromide or benzyl iodide.

The resulting reaction product is a quaternary ammonium compound, which is readily crystallized in suitable solvents, known to those skilled in the art. The crystals thus produced are quaternary ammonium salts.
20 Their identity is confirmed by standard methods, such as melting point determination, nuclear magnetic resonance (NMR) analysis and mass spectrometry.

The quaternary ammonium compounds of the invention
25 have at least one stereocenter, i.e. the carbon in position 3 (C₃ in the formula below), to which two (substituted) aryl groups are attached. Optionally, there may be a second stereocenter (when R₁, R₂ and R₃ all are different), the positively charged quaternary ammonium
30 nitrogen atom. See the general formula:



wherein Ar_1 and Ar_2 denote (substituted) aryl groups, R_1 , R_2 , R_3 and X^- are as above, and C_1 , C_2 and C_3 denote individual carbon atoms in the propylammonium backbone. Accordingly, stereoisomers (enantiomers and/or

5 diastereomers) are produced. All stereoisomers have useful activity. Therefore, the invention includes use of each stereoisomer separately, as well as mixtures thereof. Specifically, the stereoisomers in which the C_3 carbon stereocenter is in the (R) form have useful

10 activity. Moreover, the stereoisomers in which the C_3 carbon stereocenter is in the (S) form have useful activity. A mixture of stereoisomers, comprising the stereoisomers in which the C_3 carbon stereocenter is in the (R) form and the stereoisomers in which the C_3 carbon

15 stereocenter is in the (S) form, also has useful activity.

The quaternary ammonium compounds of the invention are preferably administered as salts with a

20 pharmaceutically acceptable acid. Where R_4 is $-H$, the compounds can be isolated as internal salts, which have a phenoxide anion to balance the positive charge on the quaternized nitrogen. The preferred pharmaceutically acceptable salts include salts of the following acids:

25 tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)_n-COOH$ where n is 1 thru 4, $HOOC-CH=CH-COOH$, and benzoic. For other acceptable salts, see Int. J. Pharm., 33, 201-217 (1986).

30 Particularly preferred salts are chloride, iodide and bromide salts, especially bromide salts and iodide salts.

Accordingly, X^- represents an anion of a pharmaceutically acceptable acid. Preferably, X^- is selected from the following anions: tartrate, chloride,

35 bromide, iodide, sulfate, phosphate(s), nitrate, citrate, methanesulfonate, carboxylates with from two to six

carbon atoms, dicarboxylates with from two to six carbon atoms, maleate, fumarate, and benzoate. It is preferred that X represents chloride, iodide or bromide, more preferred iodide or bromide.

5

The substituents R_1 , R_2 , R_3 may be the same or different. They are selected from the group comprising C_1 - C_6 alkyls, preferably C_1 - C_5 alkyls, straight or branched, optionally substituted with phenyl or hydroxyl, or both. Thus, R_1 , R_2 , R_3 independently represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, or isohexyl, optionally substituted with phenyl or hydroxyl, or both.

It is preferred that at least one of the substituents R_1 , R_2 , R_3 represents a C_1 - C_3 alkyl, straight or branched, i.e. methyl, ethyl, propyl, or isopropyl. It is particularly preferred that one of the substituents R_1 , R_2 , R_3 represents methyl or ethyl, preferably methyl. It is also preferred that at least one, more preferred two, of the substituents R_1 , R_2 , R_3 represent(s) isopropyl. It is especially preferred that R_1 and R_2 each represent isopropyl, and R_3 represents methyl or ethyl, preferably methyl. The substituents R_1 , R_2 , and R_3 together contain at least 3 carbon atoms. It is preferred that the substituents R_1 , R_2 , and R_3 together contain at least 4 carbon atoms, more preferred at least 5 carbon atoms, even more preferred at least 6 carbon atoms.

According to another aspect of the invention, any two of R_1 , R_2 , and R_3 may jointly form a ring structure together with the positively charged nitrogen. It is preferred that the resulting ring structure comprises from four to six carbon atoms.

The substituent R_4 is attached via an oxygen atom to its aryl ring. The $-OR_4$ group is attached to the carbon atom in position 2 in the ring, with respect to the

35

propylammonium group. The substituent R_4 may represent hydrogen, methyl or acyl ($-\text{CO}-R_{4-1}$), wherein acyl includes any one of the following: alkylcarbonyl, straight or branched, having from two to five carbon atoms, 5 alkoxycarbonyl, straight or branched, having from two to five carbon atoms, and amide, optionally mono- or independently disubstituted with alkyl, straight or branched, having from one to four carbon atom(s). Accordingly, the substituent R_{4-1} represents any one of 10 the following: C_1-C_4 alkyl, straight or branched, C_1-C_4 alkoxy, straight or branched, and $-\text{NR}_{4-2}\text{R}_{4-3}$, wherein R_{4-2} and R_{4-3} may be the same or different and represent $-\text{H}$ or $-(\text{C}_1-\text{C}_4 \text{ alkyl})$, straight or branched. Thus, the substituent R_4 may represent any one of the following: 15 hydrogen, methyl or acyl, wherein the acyl group may be acetyl (ethanoyl), propanoyl, butanoyl, isobutanoyl, pentanoyl, isopentanoyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, carbamoyl, N-methylcarbamoyl, N- 20 ethylcarbamoyl, N-propylcarbamoyl, N-butylcarbamoyl, or an N,N-dialkylcarbamoyl, wherein the alkyl groups, straight or branched, are the same or different and have from 1 to 4 carbon atoms each. Examples of N,N-dialkylcarbamoyls in this position include N,N- 25 dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, as well as N,N-diisobutylcarbamoyl, and N-propyl-N-butylcarbamoyl. It is preferred that R_4 represents hydrogen, since such compounds can be isolated as internal salts, which have a phenoxide anion to 30 balance the positive charge on the quaternized nitrogen. It is also preferred that R_4 represents alkylcarbonyl, straight or branched, having from two to five carbon atoms, e.g. acetyl (ethanoyl), propanoyl, butanoyl, isobutanoyl, pentanoyl, or isopentanoyl. Moreover, it is 35 preferred that R_4 represents methyl.

The substituent R_5 may be connected to any, otherwise not substituted, carbon atom in its aryl ring. In other words, R_5 is not connected to any of the carbon atoms to which the $-OR_4$ group or the (substituted) phenylpropylammonium group is connected, but R_5 may be connected to any one of the remaining four carbon atoms in its aryl ring.

R_5 may represent any one of the following: hydrogen, methoxy, hydroxyl, carbamoyl, sulphamoyl, halogen (fluorine, chlorine, bromine, iodine), trifluoromethyl or an alkyl group, straight or branched, having from one to four carbon atoms. Optionally, this alkyl group may be mono- or independently disubstituted with hydroxyl, with an alkoxy group, straight or branched, having from one to four carbon atoms, with carboxyl, or with alkoxycarbonyl ($-\text{CO}-\text{O}-(\text{C}_1-\text{C}_3 \text{ alkyl})$), straight or branched, having from one to four carbon atoms. It is preferred that R_5 represents any one of the following: hydrogen, bromine, chlorine, methyl or hydroxymethyl. It is particularly preferred that R_5 represents methyl. If R_5 does not represent hydrogen, it is preferred that R_5 is situated opposite the $-OR_4$ group, i.e. at the carbon atom in position 5 in the ring, with respect to the propylammonium group.

The substituents R_6 and R_7 are connected to the same aryl ring, which is different from the aryl ring to which the substituents R_4 and R_5 are connected. R_6 and R_7 may be the same or different. R_6 and R_7 may independently represent any one of the following: hydrogen, methoxy, hydroxyl, carbamoyl, sulphamoyl, halogen (fluorine, chlorine, bromine, iodine), trifluoromethyl or an alkyl group, straight or branched, having from one to four carbon atoms. Optionally, this alkyl group may be mono- or independently disubstituted with hydroxyl, with an alkoxy group, straight or branched, having from one to four carbon atoms, with carboxyl, or with alkoxycarbonyl

(-CO-O-(C₁-C₃ alkyl)), straight or branched, having from one to four carbon atoms.

It is preferred that at least one, preferably both, of R₆ and R₇ represents hydrogen. When one, but not both, of R₆ and R₇ represents hydrogen, it is preferred that the other (R₇ or R₆, respectively) is attached to the carbon atom in position 2 in the ring, with respect to the propylammonium group. When neither R₆ nor R₇ represent hydrogen, it is preferred that one is attached to the carbon atom in position 2 and the other to any one of the carbon atoms in positions 3, 4, or 5, respectively, in the ring, with respect to the propylammonium group.

The novel class of compounds according to the present invention are antimuscarinic agents.

"Antimuscarinic agents" refer to muscarinic receptor antagonists. Examples of known antimuscarinic agents include tolterodine, hydroxytolterodine, 2-(diisopropylamino)ethyl-1-phenylcyclopentanecarboxylate, propiverine, oxybutynin, trospium, darifenacin, temiverine, ipratropium, and tiotropium.

Propiverine is 1-methyl-4-piperidyl .alpha., .alpha.-diphenyl-.alpha.-(n-propoxy)acetate and is disclosed in East German Patent 106,643 and in CAS 82-155841s (1975). Oxybutynin is 4-(diethylamino)-2-butynylalphaphenylcyclohexaneglycolate and is disclosed in UK Patent 940,540. Trospium is 3alpha-hydroxyspiro[1alphaH,5alphaH-nortropane-8,1'pyrrolidinium]chloride benzilate and is disclosed in US Patent 3,480,623. Darifenacin is 3-Pyrrolidineacetamide, 1-[2-(2,3-dihydro-5-benzofuranyl)ethyl]-alpha, alpha-diphenyl-, and is disclosed in US Patent 5,096,890. Temiverine is benzeneacetic acid, .alpha. cyclohexyl-.alpha.-hydroxy-, 4-(diethylamino)-1,1-dimethyl-2-butynyl ester and is disclosed in US Patent 5,036,098. Ipratropium is 8-

isopropylnoratropine methobromide and is disclosed in US Patent 3,505,337. Tiotropium is (1-alpha,2-beta,4-beta,5-alpha,7-beta)-7-[(hydroxydi-(2-thienyl)acetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane and is disclosed in EP 418,716.

The compounds of the invention have anti-cholinergic properties. Thus, they are useful for the treatment of acetylcholine-mediated disorders. In particular, they are useful for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, and rhinorrhea due to the common cold.

"Asthma" refers to a chronic lung disease causing bronchoconstriction (narrowing of the airways) due to inflammation (swelling) and tightening of the muscles around the airways. The inflammation also causes an increase in mucus production, which causes coughing that may continue for extended periods. Asthma is characterized by recurrent episodes of breathlessness, wheezing, coughing, and chest tightness, termed exacerbations. The severity of exacerbations can range from mild to life threatening. The exacerbations can be a result of exposure to e.g. respiratory infections, dust, mold, pollen, cold air, exercise, stress, tobacco smoke, and air pollutants.

"COPD" refers to Chronic Obstructive Pulmonary Disease, primarily associated with past and present cigarette smoking. It involves airflow obstruction, mainly associated with emphysema and chronic bronchitis. Emphysema causes irreversible lung damage by weakening and breaking the air sacs within the lungs. Chronic Bronchitis is an inflammatory disease, which increases mucus in the airways and bacterial infections in the bronchial tubes, resulting in obstructed airflow.

"Allergic rhinitis" refers to acute rhinitis or nasal rhinitis, including hay fever. It is caused by

allergens such as pollen or dust. It may produce sneezing, congestion, runny nose, and itchiness in the nose, throat, eyes, and ears.

"Rhinorrhea due to the common cold" refers to watery discharge from the nose in association with a virus infection, such as the common cold. The rhinorrhea may be caused by rhinitis due to a virus infection (such as the common cold).

"Urinary disorders" and symptoms thereof include some or all of the following: urgency, frequency, incontinence, urine leakage, enuresis, dysuria, hesitancy, and difficulty of emptying bladder. In particular, urinary disorders include urinary incontinence, caused by e.g. unstable or overactive urinary bladder.

Overactive urinary bladder encompasses variants of urinary disorders, including overactive detrusor (detrusor instability, detrusor hyperreflexia) and sensory urgency, as well as symptoms of detrusor overactivity, e.g. urge incontinence, urgency, urinary frequency, and LUTS (Lower Urinary Tract Symptoms), including obstructive urinary symptoms, such as slow urination, dribbling at the end of urination, inability to urinate and/or the need to strain to urinate at an acceptable rate, or irritating symptoms such as frequency, dry overactive bladder, and/or urgency).

Other conditions are also included, which give rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia and mixed incontinence. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia), including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet

obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis.

5

The compounds of the present invention are used to treat mammals, including man and horse. It is preferred that the mammal is a human.

10

The compounds according to the invention, in the form of free base or salts with pharmaceutically acceptable acids, or solutions thereof, can be brought into suitable dosage forms, such as compositions for administration through the oral, rectal, transdermal, parenteral, nasal, or pulmonary route in accordance with accepted pharmaceutical procedures. In particular, the compositions may be administered via inhalation or insufflation. Such pharmaceutical compositions according to the invention comprise the compounds according to the invention in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives such as stabilizers, wetting agents, emulsifiers, flavoring agents, buffers, binders, disintegrants, lubricants, glidants, antiadherents, propellants, and the like.

30

The novel compounds according to the present invention can be administered in any suitable way. The compounds according to the invention can be made up in

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solid or liquid form, such as tablets, capsules, powders, syrups, elixirs and the like, aerosols, sterile solutions, suspensions or emulsions, and the like. They are advantageously administered via inhalation or
5 insufflation. When the administration form is inhalation or insufflation, the compounds are preferably in the form of either an aerosol or a powder.

The term "effective amount" refers to a
10 therapeutically effective amount for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, rhinorrhea due to the common cold, or urinary disorder. The terms "therapy" and "therapeutically" encompass all kinds of treatments, including prophylaxis.
15 In particular, "therapeutically effective" means that it is effective for anti-cholinergic treatment.

The dosage of the specific compound according to the invention will vary depending on its potency, the mode of administration, the age and weight of the patient and the
20 severity of the condition to be treated.

Doses administered by inhaler, such as a dry powder inhaler (DPI) or a metered-dose inhaler (MDI), are preferably given as one or two puffs, preferably comprising the total daily dose. For a human subject, it
25 is preferred that the dosage is in the range of from 1 microgram (1 μ g) to one milligram (1 mg).

Doses administered by nebulizer solution are generally higher than doses administered by inhaler. For a human subject, it is preferred that the total dosage
30 given by nebulizer solution is in the range of from 1 microgram (1 μ g) to ten milligrams (10 mg).

Thus, a clinically effective amount of the compounds according to the invention is from about 1 μ g to about 10 mg. It is preferred that the effective amount is from
35 about 1 μ g to about 1 mg, preferably from about 0.01 mg to about 1 mg.

The compounds of the invention can be administered from one to four times daily. It is preferable to administer the compounds once or twice daily, more preferable once daily.

5

The dosage form for inhalation can be an aerosol. The minimum amount of an aerosol delivery is about 0.2 ml and the maximum aerosol delivery is about 5 ml. The concentration of the compounds according to the invention may vary as long as the total amount of spray delivered is within the about 0.2 to about 5 ml amount and it delivers an effective amount. It is well known to those skilled in the art that if the concentration is higher, one gives a smaller dose to deliver the same effective amount.

15

The non-active ingredient or carrier can be just (sterile) water with the pH adjusted to where the active pharmaceutical agent is very soluble. It is preferred that the pH be at or near 7. Alternatively and preferably, the non-active carrier agent should be physiological saline with the pH adjusted appropriately. Aerosols for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many aerosols for treating asthma.

20

Alternatively, the dosage form for inhalation can be a powder. Powders for inhalation of various pharmaceutical agents are well known to those skilled in the art, including many powders for treating asthma. When the dosage form is a powder, the compounds according to the invention can be administered in pure form or diluted with an inert carrier. When an inert carrier is used, the compounds according to the invention are compounded such that the total amount of powder delivered delivers an "effective amount" of the compounds according to the invention. The actual concentration of the active

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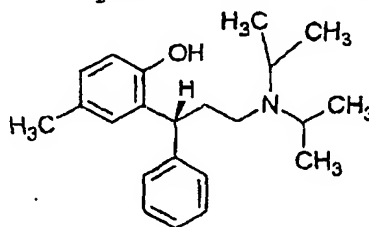
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compound may vary. If the concentration is lower, then more powder must be delivered; if the concentration is higher, less total material must be delivered to provide an effective amount of the active compound according to the invention.

For treatment of rhinitis, in particular rhinitis due to the common cold, the compounds according to the invention can advantageously be administered in combination with steroids, cromoglycates, and decongestants (alpha agonists). Such combination therapies are useful in the treatment of rhinorrhea due to the common cold.

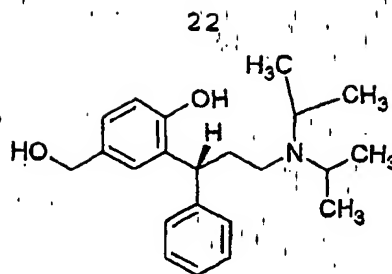
The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

Tolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol, also known as N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, a compound of the formula:



(R)-stereoisomer

Hydroxytolterodine refers to 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenol, a compound of the formula:



Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

10 Examples

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

All temperatures are in degrees Celsius.

Ether refers to diethyl ether.

25 Physiological saline refers to an 0.9% aqueous sodium chloride solution.

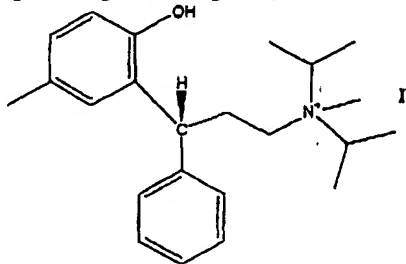
When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

5 EXAMPLE 1 Tolterodine Free Base

Tolterodine tartrate (2.1 g) is mixed with water (45 ml) and toluene (2.5 ml). Sodium carbonate (800 mg) is added to the slurry. Sodium hydroxide (2.0 N, 1.5 ml) is added. The mixture is extracted three times with toluene
10 (3 ml), saving the organic phase. Anhydrous potassium carbonate is added to the organic phase dissolve the tolterodine tartate, giving the title compound in solution.

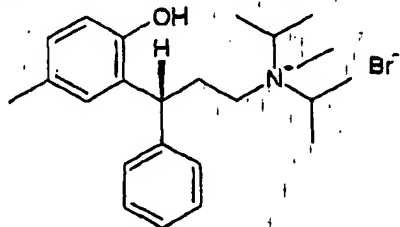
15 EXAMPLE 2 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



To tolterodine free base (from Example 1, 0.5 M, 2.5 ml) in toluene is added methyl iodide (1 ml).
20 Acetonitrile (5 ml) is added to the mixture and stirred over night at 20-25°C. The solvent is removed by blowing dry nitrogen. Acetone (1 ml) and hexane (2 ml) are added and the mixture is filtered at 20-25°C to give the title compound. Anal Calcd for C₂₃H₃₄INO: C, 59.10; H, 7.33; N,
25 3.00. Found: C, 59.00; H, 7.44; N, 3.00. The identity of the compound has been further verified and characterised by NMR analysis, mass spectrometry, and melting point determination.

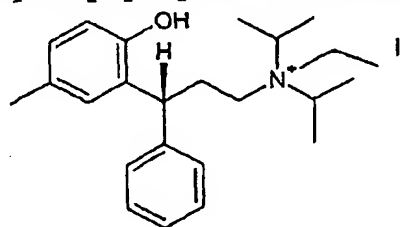
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EXAMPLE 3 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



A sealed mixture of methyl bromide (100 g) and 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (14 g) in acetone (100 ml) is stirred at 20-25°C for 4 days. The mixture is cooled to -10°C and the precipitate is filtered off and washed with ether and dried to give the title compound, mp 189-191°C (dec). Anal Calcd for $C_{23}H_{34}BrNO$: C, 65.71; H, 8.15; Br, 19.00; N, 3.33. Found: C, 65.61; H, 8.34; Br, 19.12; N, 3.32. $[\alpha]_D$ (c=1, MeOH) +25°C. 1H NMR $[(CD_3)_2SO]$ δ 1.25, 2.18, 2.48, 2.81, 3.05, 3.89, 4.22, 6.70, 6.83, 7.08, 7.19, 7.33, and 9.3.

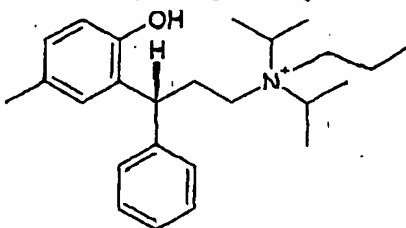
EXAMPLE 4 (3R)-N-Ethyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with ethyl iodide, the title compound is obtained.

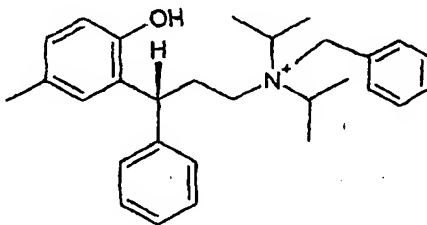
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EXAMPLE 5 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-N-propylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with propyl iodide, the title compound is obtained.

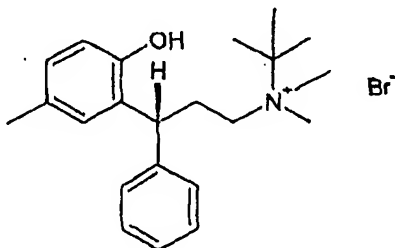
EXAMPLE 6 (3R)-N-Benzyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with benzyl iodide, the title compound is obtained.

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EXAMPLE 7 (3R)-N-(tert-Butyl)-3-(2-hydroxy-5-methylphenyl)-N,N-dimethyl-3-phenylpropan-1-aminium bromide



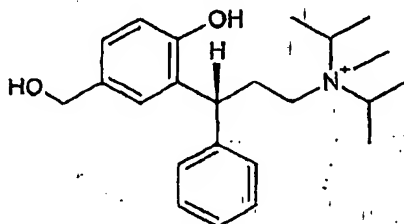
Following the general procedure of Example 2 and making non critical variations, but starting with methyl bromide

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and 2-[(1R)-3-[tert-butyl(methyl)amino]-1-phenylpropyl]-4-methylphenol, the title compound is obtained.

EXAMPLE 8 (3R)-3-[2-Hydroxy-5-

5 (hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-

10 (hydroxymethyl)phenol, the title compound is obtained.

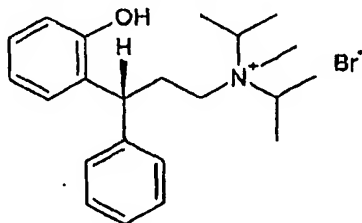
Anal Calcd for $C_{23}H_{34}INO_2$: C, 57.14; H, 7.09; N, 2.90.

Found: C, 56.33; H, 7.33; N, 2.76. HRMS Calcd 356.2589.

Found: 356.2588. 1H NMR $[(CD_3)_2SO]$ δ 1.25, 2.48, 2.81, 3.05, 3.88, 4.26, 4.35, 4.94, 6.75, 6.98, 7.20, 7.33, and 9.5.

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EXAMPLE 9 (3R)-3-(2-Hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



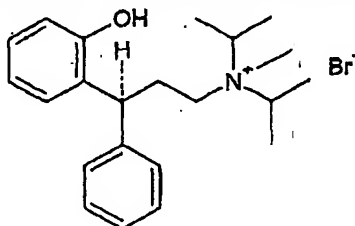
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Following the general procedure of Example 3 and making non critical variations but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

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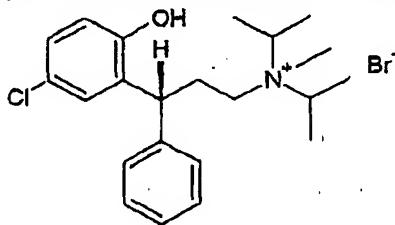
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EXAMPLE 10 (3S)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



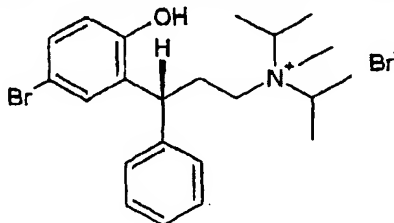
Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1S)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 11 (3R)-3-(5-Chloro-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



Following the general procedure of Example 3 and making non critical variations, but starting with 4-chloro-2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 12 (3R)-3-(5-Bromo-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide

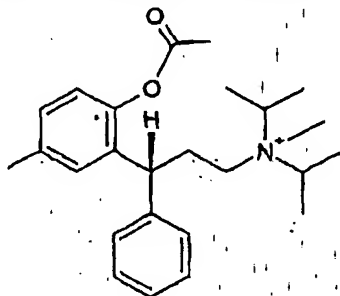


Following the general procedure of Example 3 and making non critical variations, but starting with 4-

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bromo-2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]phenol, the title compound is obtained.

EXAMPLE 13 (3R)-3-[2-(Acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



(A) 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate

10 A solution of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (0.9 g) in acetylchloride (20 ml) is stirred at room temperature for 18 h. The acetyl chloride is evaporated, ether is added, and the precipitate of 2-(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate hydrochloride is
15 filtered off; mp 126-130°C. Anal Calcd for $C_{24}H_{33}NO_2 \cdot HCl$: C, 71.35; H, 8.48; Cl, 8.78; N, 3.47. Found: C, 71.02; H, 8.30; Cl, 8.64; N, 3.43. $[\alpha]_D$ (c=1, MeOH) +11°.

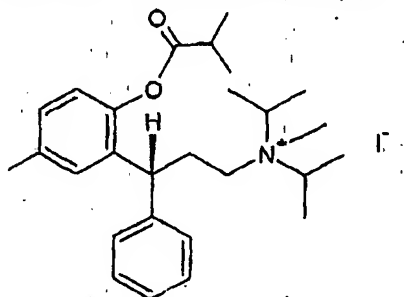
The hydrochloride salt is partitioned between ether
20 and saturated sodium bicarbonate solution. The ether phase is separated and evaporated to obtain the free base of compound (A).

(B) (3R)-3-[2-(acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide

25 Following the general procedure of Example 2 and making non critical variations, but starting with (A): 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl acetate, the title compound (B) is obtained.

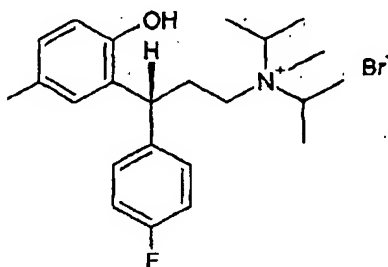
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EXAMPLE 14 (3R)-3-[2-(Isobutyryloxy)-5-methylphenyl]-
N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making
5 non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl 2-methylpropanoate, the title compound is obtained.

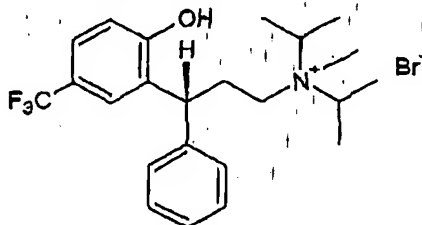
EXAMPLE 15 (3R)-3-(4-Fluorophenyl)-3-(2-hydroxy-5-
10 methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium
bromide



Following the general procedure of Example 3 and making
non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-(4-fluorophenyl)propyl]-4-
15 methylphenol, the title compound is obtained.

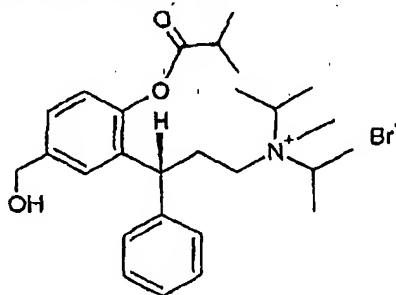
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EXAMPLE 16 (3R)-3-[2-Hydroxy-5-(trifluoromethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



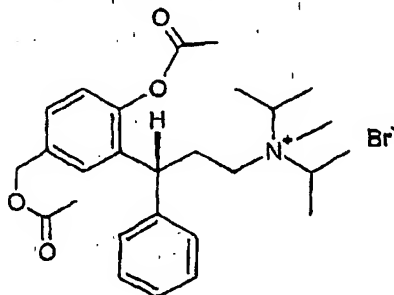
5 Following the general procedure of Example 3 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-(trifluoromethyl)phenol, the title compound is obtained.

10 EXAMPLE 17 (3R)-3-[2-(Isobutyryloxy)-5-hydroxymethylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



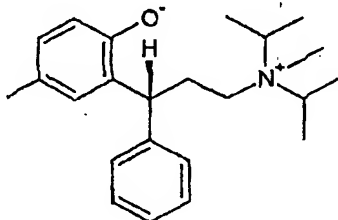
15 (3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide is acylated with isobutyryl bromide to give the title compound.

EXAMPLE 18 (3R)-3-{2-(Acetyloxy)-5-[(acetyloxy)methyl]phenyl}-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide



5 (3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide is acylated with acetyl bromide, to give the title compound.

EXAMPLE 19 2-{(1R)-3-[Diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate

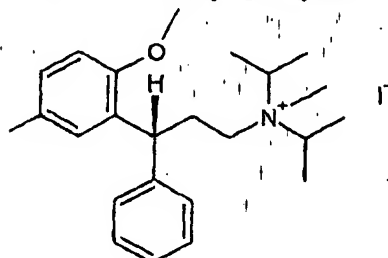


(3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide from Example 2 is
15 passed through an ion exchange column so as to remove the bromide ion and generate the title compound.

Reacting the above compound with an equivalent amount of an acid, such as methanesulfonic acid, hydrochloric acid, acetic acid, or succinic acid,
20 generates other salts of the title compound.

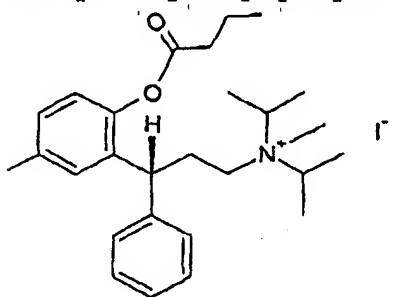
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EXAMPLE 20 (3R)-N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-N-methyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making
 5 non critical variations, but starting with (3R)-N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropan-1-amine, the title compound is obtained; mp 211 °C (dec).
 Anal Calcd for $C_{24}H_{36}INO$; C, 59.87; H, 7.54; N, 2.91.
 Found: C, 59.78; H, 7.56; N, 2.99. $[\alpha]_D$ (c = 1, MeOH)
 10 +13°.

EXAMPLE 21 (3R)-3-[2-(Butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



15 (A) 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate

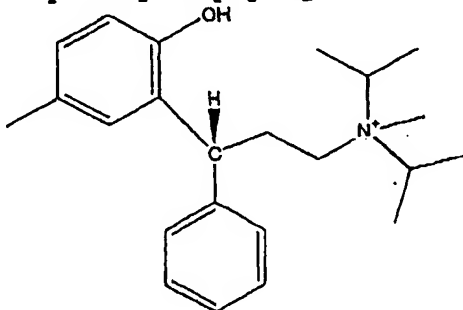
A solution of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenol (1.0 g) in butyryl chloride (5 ml) is heated under reflux for 90 min. Ether is added,
 20 and the precipitate of 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate hydrochloride is filtered off; mp 116-119 °C. Anal Calcd for $C_{26}H_{37}NO_2 \cdot HCl$:
 C, 72.28; H, 8.86; Cl, 8.21; N, 3.24. Found: C, 72.25; H, 8.71; Cl, 8.17; N, 3.25. $[\alpha]_D$ (c = 1, MeOH) +20°.

The hydrochloride salt is partitioned between ether and saturated sodium bicarbonate solution. The ether phase is separated and evaporated to obtain the free base of the title compound (A).

(B) (3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide

Following the general procedure of Example 2 and making non critical variations, but starting with (A): 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-methylphenyl butyrate, the title compound is obtained; mp 175 °C (dec). Anal Calcd for $C_{27}H_{40}INO_2$: C, 60.33; H, 7.50; N, 2.61. Found: C, 60.37; H, 7.52; N, 2.58.

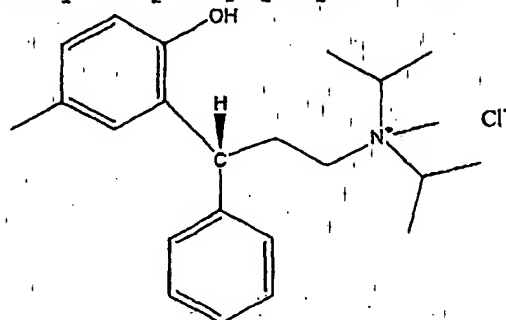
EXAMPLE 22 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



(3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide (from Example 22) was hydrolysed with methanol, resulting in the title compound.

34

EXAMPLE 23 (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride

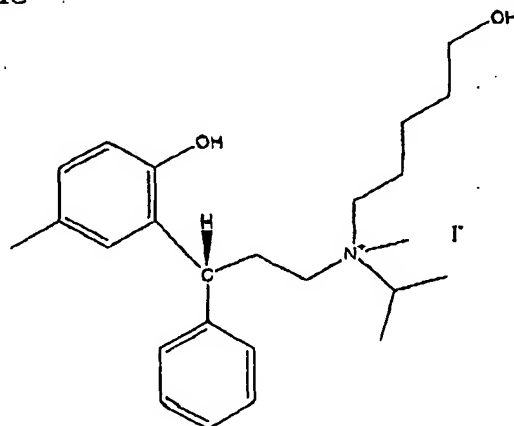


A solution of (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide (4.2 g, 0.01 mol) in water (50 ml) is neutralized by addition of 1 equivalent of 2 N sodium hydroxide solution (5.0 ml). The solvent is evaporated, and the residual oil is chromatographed to separate 2-((1R)-3-

10 [diisopropyl(methyl)ammonio]-1-phenylpropyl)-4-methylbenzenolate from the sodium bromide. The product is reconstituted in acetone, and a solution of hydrogen chloride in ethyl acetate is added to give a precipitate of the title compound.

15

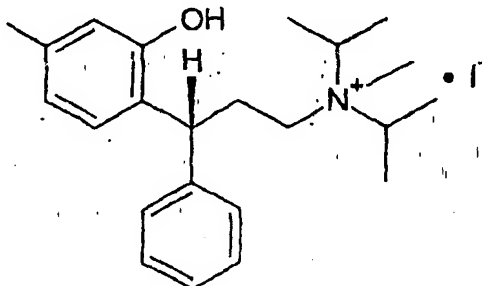
EXAMPLE 24 5-Hydroxy-N-[(3R)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-N-isopropyl-N-methylpentan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-[(5-hydroxypentyl)(isopropyl)amino]-1-phenylpropyl]-4-methylphenol, the title compound is obtained.

5

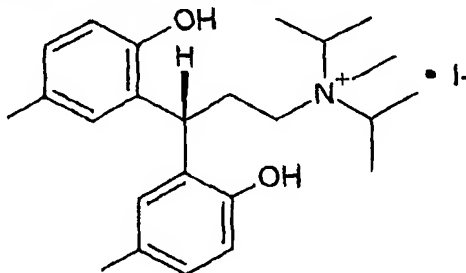
EXAMPLE 25 (3R)-3-(2-Hydroxy-4-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



Following the general procedure of Example 2 and making non critical variations, but starting with 2-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-5-methylphenol, the title compound is obtained.

EXAMPLE 26 3,3-bis(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide

15

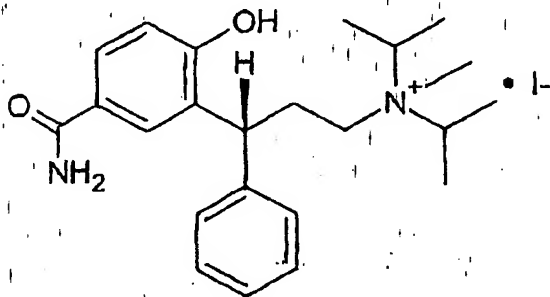


Following the general procedure of Example 2 and making non critical variations, but starting with 2-[3-(diisopropylamino)-1-(2-hydroxy-5-methylphenyl)propyl]-4-methylphenol, the title compound is obtained.

20

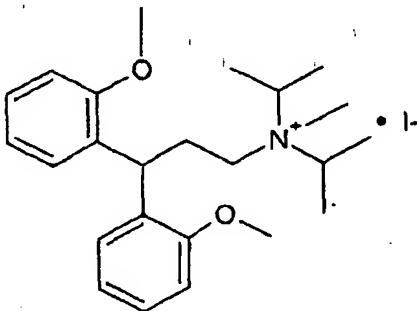
36

EXAMPLE 27 (3R)-3-[5-(Aminocarbonyl)-2-hydroxyphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



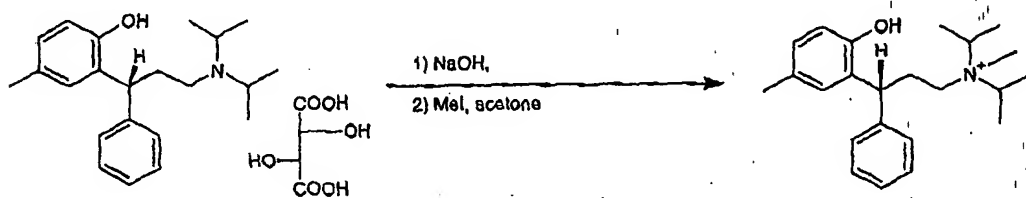
5 Following the general procedure of Example 2 and making non critical variations, but starting with 3-[(1R)-3-(diisopropylamino)-1-phenylpropyl]-4-hydroxybenzamide, the title compound is obtained.

10 EXAMPLE 28 3,3-bis(2-Methoxyphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide



15 Following the general procedure of Example 2 and making non critical variations, but starting with N,N-diisopropyl-3,3-bis(2-methoxyphenyl)propan-1-amine, the title compound is obtained.

EXAMPLE 29 Large scale production of (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide



A 5 l erlenmyer flask was charged with 250 g (526 mmol) tolterodine tartrate, water (2000 ml), and methylene chloride (2000 ml). A solution of 84 g of 50% NaOH diluted with 200 ml of water was added, and the mixture was stirred for 1 hour. The pH was kept in the range of 8-9. Both of the two resulting phases are clear and colorless.

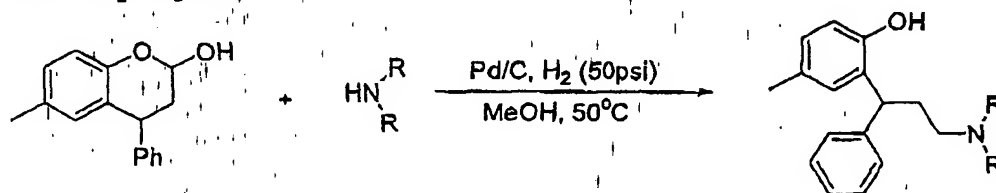
The phases were separated, and the aqueous phase was washed with methylene chloride (1000 ml). The combined organic phases were concentrated on the rotovap (60°C bath). The weight of the residue was determined. The residue was dissolved in acetone (1000 ml), and 263 ml (2.84 mol) methyl iodide was added, all in one portion. The mixture was stirred at room temperature overnight.

The resulting slurry was filtered, washed with acetone (250 ml) and dried in the vacuum oven at 50°C overnight.

This provided 230 g of the desired product, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide.

EXAMPLE 30 Cyclic amine intermediates

The following general reductive amination procedure was employed:



5 wherein Ph represents a phenyl group, and R represents an alkyl group according to the following Table I.

Briefly, palladium on activated carbon (1.76 g, 5% by weight, Aldrich 20,568-0) was charged to a hydrogenation vessel under nitrogen, followed by a MeOH
 10 (20 mL) solution of a racemic lactol (6-methyl-4-phenyl-2-chroman-1-ol, see formula above) (4 g, 16.64 mmol) and a secondary amine (42 mmol, 2.5 equiv). The vessel was filled with hydrogen (50 psi), and the reaction mixture was stirred vigorously at 50°C overnight. The
 15 heterogeneous reaction mixture was filtered through celite. The resulting methanolic solution was concentrated under vacuum.

Pure cyclic amines according to the following table I were obtained after trituration with hexanes.

20

Table I Intermediate compounds		
R	Resulting compound	Yield (%)
(CH ₂) ₄	4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol	71
(CH ₂) ₅	4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol	33
(CH ₂) ₆	2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol	29

Characterization of 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol:

39

^1H NMR (CDCl_3): δ 1.90 (m, 4H), 2.09 (s, 4H), 2.25-2.45 (m, 2H), 2.57 (m, 2H), 2.63-2.78 (m, 3H), 4.55 (dd, 1H, $J=12$ Hz, $J=3$ Hz), 6.47 (s, 1H), 6.85 (s, 2H), 7.19-7.26 (m, 2H), 7.30 (m, 3H), 11.23 (s, 1H).

5 ^{13}C NMR (CDCl_3): δ 19.8, 26.0, 33.5, 39.9, 53.5, 54.3, 125.8, 127.3, 128.1, 128.4, 128.7, 131.2, 145.0, 153.0.

ESI mass spectrum: 296 $[\text{M}+1^+]$, 297 $[\text{M}+2^+]$.

Characterization of 4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol:

10 ^1H NMR (CDCl_3): δ 1.52-1.53 (m, 2H), 1.62-1.81 (m, 4H), 1.98 (t, 1H, $J=10$ Hz), 2.09 (s, 3H), 2.26-2.60 (m, 6H), 4.46 (dd, 1H, $J=13$ Hz, $J=3$ Hz), 6.47 (s, 1H), 6.85 (d, 2H, $J=0.9$ Hz), 7.19-7.24 (m, 2H), 7.30-7.35 (m, 3H), 11.24 (s, 1H).

15 ^{13}C NMR (CDCl_3): δ 20.9, 24.4, 25.4, 31.3, 38.4, 53.8, 54.7, 61.0, 102.2, 117.9, 126.3, 128.1, 128.4, 128.6, 129.3, 129.4, 131.4, 145.2, 154.3.

ESI mass spectrum: 310 $[\text{M}+1^+]$, 311 $[\text{M}+2^+]$

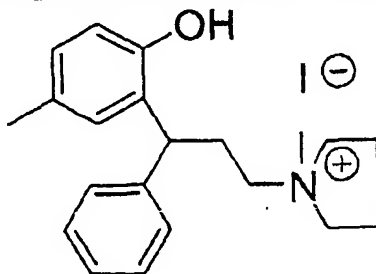
20 Characterization of 2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol:

^1H NMR (CDCl_3): δ 1.60-1.65 (m, 4H), 1.65-1.85 (m, 4H), 1.95-2.10 (m, 4H), 2.30-2.67 (m, 6H), 2.70-2.80 (m, 2H).

25 ^{13}C NMR (CDCl_3): δ 19.6, 26.6, 26.7, 32.0, 40.7, 55.1, 55.7, 115.9, 125.8, 127.3, 128.0, 128.1, 128.5, 128.7, 131.4, 145.1, 153.0, 145.2, 152.8.

ESI mass spectrum: 324 $[\text{M}+1^+]$, 325 $[\text{M}+2^+]$.

EXAMPLE 31 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpyrrolidinium iodide



Methyl iodide (10 equivalents) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol of Example 30 (0.3 g, 1.02 mmol) in acetone (4 mL). The reaction mixture is stirred overnight at room temperature. The solution is concentrated to initiate the precipitation of the resulting quaternary ammonium salt. The white precipitate is filtered, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 79%.

The resulting compound was characterized:

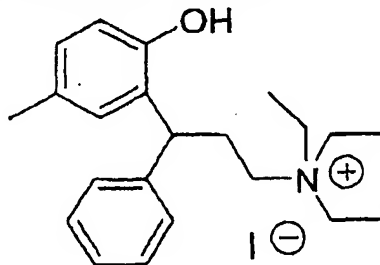
^1H NMR ($\text{MeOH}-d_4$): δ 2.05-2.18 (m, 4H), 2.20 (s, 3H), 2.46-2.62 (m, 2H), 3.08 (s, 3H), 3.14-3.40 (m, 2H), 3.40-3.62 (m, 4H), 4.40 (t, 1H, $J=7.3$ Hz), 6.68 (d, 1H, $J=8$ Hz), 6.85 (d, 1H, $J=8$ Hz), 6.98 (d, 1H, $J=1.5$ Hz), 7.16-7.23 (m, 1H), 7.30 (t, 2H, $J=7$ Hz), 7.37-7.42 (m, 2H).

^{13}C NMR ($\text{MeOH}-d_4$): δ 19.3, 21.5, 28.2, 41.5, 46.8, 63.6, 64.5, 115.2, 126.5, 127.9, 128.0, 128.4, 128.5, 128.9, 129.2, 143.4, 152.5.

Elemental analysis, $\text{C}_{21}\text{H}_{28}\text{INO}$: Found(%): C 57.64, H 6.43, I 28.77, N 3.23, O 3.88; Theory(%): % C 57.67, H 6.45, I 29.02, N 3.20, O 3.66.

ESI mass spectrum for $\text{C}_{21}\text{H}_{28}\text{NO}^+$: 310.2.

EXAMPLE 32 1-Ethyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]pyrrolidinium iodide



Ethyl iodide (10 equivalents) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-pyrrolidin-1-ylpropyl)phenol of Example 30 (0.3 g, 1.02 mmol) in acetone (4 mL). The reaction mixture is stirred

41

overnight at room temperature. The solution is concentrated to initiate the precipitation of the resulting quaternary ammonium salt. The white precipitate is filtered, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 81%. The resulting compound was characterized:

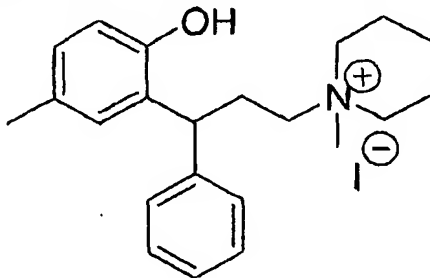
^1H NMR ($\text{MeOH}-d_4$): δ 1.24 (t, 3H, $J=7$ Hz), 2.0-2.18 (m, 4H), 2.20 (s, 3H), 2.40-2.63 (m, 2H), 3.08-3.25 (m, 2H), 3.35-3.60 (m, 6H), 4.38 (t, 1H, $J=7.5$ Hz), 6.70 (d, 1H, $J=8$ Hz), 6.85 (d, 1H, $J=8$ Hz), 7.0 (d, 1H, $J=1.4$ Hz), 7.16-7.23 (m, 1H), 7.30 (t, 2H, $J=7$ Hz), 7.37-7.42 (m, 2H).

^{13}C NMR ($\text{MeOH}-d_4$): δ 8.0, 19.5, 21.5, 28.0, 41.9, 54.7, 58.0, 64.5, 117.8, 126.4, 127.9, 128.1, 128.4, 128.7, 128.9, 129.2, 143.6, 152.8.

Elemental analysis, $\text{C}_{22}\text{H}_{30}\text{INO}$: Found(%): C 58.17, H 6.65, I 27.79, N 3.10, O 3.62; Theory(%): C 58.54, H 6.70, I 28.11, N 3.10, O 3.54.

ESI mass spectrum for $\text{C}_{22}\text{H}_{30}\text{NO}^+$: 324.2.

EXAMPLE 33 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpiperidinium iodide



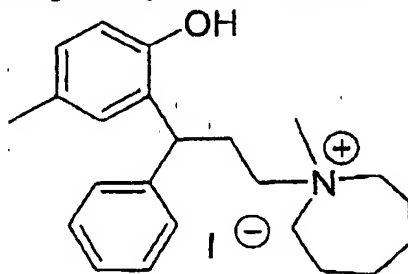
Methyl iodide (3.42 g, 1.5 mL, 0.024 mol) was added to a solution of the free base 4-methyl-2-(1-phenyl-3-piperidin-1-ylpropyl)phenol of Example 30 (0.3 g, 0.97 mmol) in a mixture of acetonitrile (6 mL) and acetone (2 mL). The reaction mixture was stirred overnight at room temperature. The solution was concentrated to initiate

precipitation of the resulting quaternary ammonium salt. The white precipitate was filtered out, washed with chloroform and diethyl ether and dried under vacuum to give 0.397 g (90%) of the title compound.

5 Characterization of the obtained compound:

^1H NMR (MeOH- d_4): δ 1.57-1.84 (m, 6H), 2.19 (s, 3H), 2.46-2.64 (m, 2H), 3.06 (s, 3H), 3.14-3.4 (m, 6H), 4.39 (t, 1H, $J=7.3\text{ Hz}$), 6.68 (d, 1H, $J=8\text{ Hz}$), 6.85 (dd, 1H, $J=8\text{ Hz}$, $J=1.5\text{ Hz}$), 7.0 (d, 1H, $J=1.5\text{ Hz}$), 7.18 (t, 1H, $J=8\text{ Hz}$),
 10 7.29 (t, 1H, $J=7.4\text{ Hz}$), 7.37-7.4 (m, 5H).
 ^{13}C NMR (MeOH- d_4): δ 19.5, 19.7, 19.8, 20.7, 26.7, 41.5, 60.9, 61.2, 114.0, 115.1, 126.3, 127.9, 128.0, 128.4, 128.5, 128.9, 129.2, 143.4, 152.4.

15 EXAMPLE 34 1-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylazepanium iodide



Methyl iodide (10 equivalents) was added to a solution of the free base 2-(3-azepan-1-yl-1-phenylpropyl)-4-methylphenol of Example 30 (0.3 g, 1.02 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred overnight at room temperature. The solution was concentrated to initiate precipitation of the resulting quaternary ammonium salt. The white precipitate was
 20 filtered out, washed with diethyl ether and dried under vacuum to give a quaternized salt.

White crystals were obtained with a yield of 77%. The resulting compound was characterized:

^1H NMR (MeOH- d_4): δ 1.6-2.0 (m, 8H), 2.01 (s, 3H), 2.40-2.70 (m, 2H), 3.10 (s, 3H), 3.15-3.60 (m, 6H), 4.38 (t,
 30

1H, J=7 Hz), 6.68 (d, 1H, J=8Hz), 6.88 (d, 1H, J=8 Hz),
7.05 (s, 1H), 7.18-7.24 (m, 1H), 7.25-7.40 (m, 5H).

¹³C NMR (MeOH-d₄): δ 20.8, 22.4, 27.5, 41.6, 50.2, 59.2,
63.8, 64.5, 64.8, 117.5, 126.3, 127.95, 128.03, 128.4,
5 128.6, 128.9, 129.2, 143.4, 152.5.

ESI mass spectrum for C₂₃H₃₂NO⁺: 338.2.

The usefulness of the compounds according to the
10 invention is further illustrated by the following
examples.

EXAMPLE I Binding data

15 Muscarinic receptor subtype M₁-M₅ binding assays were
carried out. Briefly, [3]H-methylscopolamine was allowed
to bind to membranes from various recombinant mammalian
cell lines, each with an over-expression of a particular
receptor subtype. An equilibrium radioligand displacement
20 assay was performed using the title compound of example
2, (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-
methyl-3-phenylpropan-1-aminium iodide (a quaternary
ammonium compound according to the invention), and for
comparison the following anticholinergic agents:
25 tolterodine, hydroxytolterodine, ipratropium, and
atropine. The resulting K_i values, displayed in Table II,
are averages of duplicate samples at each dose in an 11-
point dose-response curve, using half-log intervals.

Table II K_i values (nM)

Receptor subtype	Displacing compound				
	(3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide	Tolterodine	Hydroxytolterodine	Ipratropium	Atropine
M_1	0.33	0.87	1.5	0.46	0.25
M_2	0.45	0.73	0.33	0.17	0.43
M_3	0.20	2.1	1.4	0.38	0.87
M_4	0.39	1.5	1.4	0.42	0.48
M_5	0.25	0.55	0.48	0.54	0.47

Thus, the title compound of example 2, (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, according to the invention has high affinity and little or no selectivity for any of the muscarinic receptor M_1 - M_5 subtypes. Obtained K_i values for (3R)-3-(2-Hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide are in the same range as K_i values for tolterodine, hydroxytolterodine, ipratropium, and atropine.

EXAMPLE II Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Female BALB/c mice, weight range 19-22 g, were obtained from Charles River Laboratories (Kingston, NC). They received food and water *ad libitum*. All procedures in these studies were in compliance with the Animal Welfare Act Regulation, 9CFR Parts 1 and 2, Publication (NIH) 85-23, 1985.

Compounds for aerosol administration were prepared in sterile Dulbecco's Phosphate Buffered Saline.

Mice were placed in a carousel-style, nose only, exposure chamber and allowed to inhale aerosols for five minutes, using an ICN SPAG-2 nebulizer. This nebulizer generates a mean aerosol particle size of 1.3 microns at a rate of approximately 0.25 ml/minute.

Ten minutes, 4 hours, 8 hours, 24 hours, 36 hours or 48 hours later, the mice were moved to whole body plethysmograph chambers. Bronchoconstriction was induced in mice by administration of an 80 mg/ml methacholine (MC) aerosol into the plethysmograph chambers for 5 minutes. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation treatment with vehicle, or 80 mg/ml methacholine following inhalation treatment with 0.072, 0.144, or 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, or 80 mg/ml methacholine following inhalation treatment with 1.24 mg/ml ipratropium bromide. The average enhanced pause (lung resistance) was determined. In order to determine the baseline, saline aerosol (without methacholine) was also separately administered to the mice.

The results are shown in fig 1 (1.44 mg/ml of the title compound of example 2 and 1.24 mg/ml ipratropium bromide), fig 2 (0.144 mg/ml of the title compound of example 2), and fig 3 (0.072 mg/ml of the title compound of example 2).

Increasing doses of the title compound of example 2 produce increasing durations of action. In fig 1, inhalation of aerosols generated from a solution containing 1.44 mg/ml of the title compound of example 2 produced a complete block of methacholine-induced bronchoconstriction through 36 hours following administration. Ipratropium bromide (1.24 mg/ml) did not

display an equally sustained action. Inhalation of aerosols generated from solutions containing 0.144 mg/ml (fig 2) or 0.072 mg/ml (fig 3), respectively, of the title compound of example 2 prevented methacholine-induced bronchoconstriction through 24 or 8 hours, respectively, following administration.

EXAMPLE III Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

10 Female BALB/c mice were obtained and fed as in example II. Compounds were prepared and administered to the mice (aerosol) as in example II.

 Ten minutes, 30 minutes, 1 hour, 2 hours or 4 hours later, the mice were placed in plethysmograph chambers, and bronchoconstriction was induced in the mice by administration of an 80 mg/ml methacholine aerosol. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation with vehicle, or 80 mg/ml methacholine following inhalation treatment with 1.46 mg/ml tolterodine, or 80 mg/ml methacholine following inhalation treatment with 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide.

25 The results are shown in fig 4. It is obvious from fig 4 that the title compound of example 2 has a pronounced effect on lung resistance. In addition, the bronchodilatory effects of the title compound of example 2 exhibit a prolonged duration.

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EXAMPLE IV Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

 Female BALB/c mice were obtained and fed as in example II. Compounds were prepared and administered to the mice (aerosol) as in example II.

Ten minutes, 2 hours, 4 hours, 8 hours or 24 hours later, the mice were placed in plethysmograph chambers, and bronchoconstriction was induced in the mice by administration of an 80 mg/ml methacholine aerosol. The mice were allowed to inhale an aerosol containing 80 mg/ml methacholine following inhalation with vehicle, or 80 mg/ml methacholine following inhalation with 1.44 mg/ml of the title compound of example 2, i.e. (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide, or 80 mg/ml methacholine following inhalation with 1.24 mg/ml ipratropium bromide.

The results are shown in fig 5. It can be concluded that the bronchodilatory effects of the title compound of example 2 have a longer duration when compared to ipratropium bromide.

EXAMPLE V Pharmacokinetics of inhaled quaternary ammonium salts in Balb/c mice

Blood samples were taken from the mice in example II via cardiac puncture under isoflurane anesthesia at 2.5 minutes, 10 minutes, 30 minutes, 2 hours, 4 hours, 8 hours, or 12 hours after aerosol drug treatment.

The samples were collected in tubes containing EDTA and centrifuged at 12000 x g for four minutes. Plasma was removed and stored at -70 °C until assay.

Plasma samples were extracted via a liquid/liquid extraction technique. Plasma levels of the title compound of example 2 were determined by ESI-LC/MS/MS using a PE SCIEX API 4000 mass spectrometer in positive ion mode. Chromatographically, the analyte and the internal standard were resolved on a Phenomenex Phenyl-Hexyl column using an isocratic elution. The limit of quantitation was 24 pg/ml.

Plasma concentrations of the title compound of example 2 following aerosol exposure (inhalation) are summarized in table III and fig 6.

Table III Plasma concentration

Time	Plasma concentration \pm std dev (pg/ml) following inhalation of various conc.		
	0.072 mg/ml	0.144 mg/ml	1.44 mg/ml
2.5 min	136 \pm 38	264 \pm 21	2675 \pm 389
10 min	90 \pm 1	162 \pm 11	1395 \pm 163
30 min	81 \pm 8	112 \pm 10	1120 \pm 42
2 h	41 \pm 6	55 \pm 7	245 \pm 3
4 h	14 \pm 1	40 \pm 3	157 \pm 2
8 h	-	12 \pm 1	80 \pm 2
12 h	-	-	42 \pm 2

The doses given to the lungs were proportional to the concentrations appearing in the plasma. Importantly, the systemic (plasma) exposure was very low, which indicates that the title compound of example 2 resides for a prolonged time in the lung. This correlates well with its long duration of action.

10 EXAMPLE VI (comparative) Pharmacokinetics of inhaled tolterodine in Balb/c mice

Female BALB/c mice were obtained and fed as in example II. Tolterodine L-tartrate for aerosol administration was prepared in sterile phosphate buffer solution at concentrations of 0.1, 0.5, and 1.0 mg/ml, and administered to the mice (aerosol) as in example II.

Blood samples were collected at 2.5 minutes, 15 minutes, 30 minutes, 1 hour or 2 hours after aerosol drug treatment. Blood samples were prepared as in example VI. Samples were analyzed using a PE SCIEX API 3000 mass spectrometer. Chromatographically, the analyte and the internal standard were resolved on a Zorbax ACE Phenyl column using a gradient elution. The limit of quantitation was 100pg/mL.

Figure 7 shows plasma concentrations of tolterodine following inhalation of nebulized solutions at 0.1, 0.5, or 1.0 mg/ml. Plasma levels for the 0.1 mg/ml concentration were at or below detection limits. Clearly, tolterodine is rapidly absorbed into the circulation. The plasma level of tolterodine is approximately one order of magnitude higher than the corresponding level of the title compound of example 2 (example V, fig 6).

This demonstrates that while tolterodine is rapidly spread systemically, the compounds according to the invention have an increased duration of action, with implications locally (i.e. for treating asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, or rhinorrhea due to the common cold).

EXAMPLE VII Binding data

Muscarinic receptor subtype M_1 - M_5 binding assays were performed. K_i values were determined for the title compounds of examples 3, 8, and 31-34 (all quaternary ammonium compounds according to the invention). The resulting K_i values are displayed in Table IV.

Table IV K_i values (nM)

Receptor subtype	Title compound of Example no					
	3	8	31	32	33	34
M_1	0.3	0.86	1.2	1.1	1.1	1
M_2	0.52	1.08	2.2	1.7	1.7	1
M_3	0.43	0.92	3.3	3.1	3.2	4.7
M_4	0.72	1.07	4.2	3.8	3.6	2.9
M_5	0.26	0.68	1.6	1.2	0.9	1.8

Thus, the title compounds of Example nos 3, 8, and 31-34 according to the invention have high affinity and little or no selectivity for any of the muscarinic receptor M_1 - M_5 subtypes.

EXAMPLE VIII Bronchodilatory effect of inhaled quaternary ammonium salts in Balb/c mice

Bronchoconstriction was induced in BALB/c mice by administration of methacholine. The title compounds of Examples 3, 8, and 31-34 (all quaternary ammonium compounds according to the invention) were administered to the mice via inhalation of 1 mg/mL (free base equivalents (FBE)) of each compound. The resulting inhibition of methacholine-induced bronchoconstriction was determined at 10 min as well as 24 h and 48 h, or 36 h, after dosing. The results are displayed in the following Table V.

Table V

Title compound of example no (1 mg/mL FBE)	% inhibition of bronchoconstriction after			
	10 min	24 h	36 h	48 h
3	100		93	
8	82	60		15
31	100		0	
32	100		17	
33	100		0	
34	100		0	

15

EXAMPLE A

A 65 year old female with a history of chronic COPD with FEV₁ of 1.5 liters is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide in an aerosol formulation, 1 mg every 12 hr continuously for dyspnea. After two weeks of therapy, dyspnea tolerance is improved.

EXAMPLE B

A 50 year old male with a history of chronic COPD with FEV₁/FVC of 60% is treated with (3R)-3-(2-hydroxy-5-

methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide in an aerosol formulation, 2 mg every 8 hr continuously for dyspnea. After a week of treatment, the FEV₁/FVC ratio improves to about 65%.

5

EXAMPLE C

A 25 year old female with a history of asthma with a morning peak flow of less than 2 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide powder, 0.1 mg every 8 hr continuously. Treatment improves the peak flow to 4-5 l/sec.

10

EXAMPLE D

A 35 year old male with a history of severe asthma with a morning peak flow of 5 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide powder, 6 mg once a day continuously. After a week of treatment, the peak flow improves to 9 l/sec.

15

20

EXAMPLE E

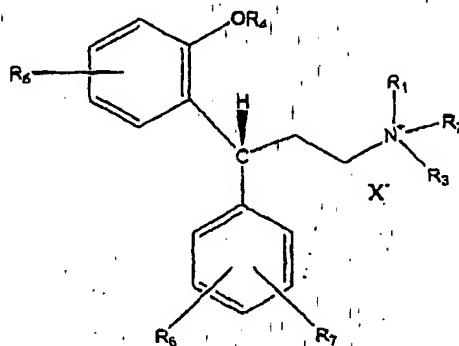
A 45 year old female with a history of severe asthma with a morning peak flow of less than 3 l/sec is treated with (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide in an aerosol formulation, 2 mg three times daily continuously. After a week of treatment the peak flow improves to 6 l/sec.

25

30

CLAIMS

1. A quaternary ammonium compound of the formula



and any stereoisomers thereof, wherein

R_1 , R_2 and R_3 independently represent C_1 - C_6 alkyl, optionally substituted with phenyl or hydroxyl, or both, and wherein any two of R_1 , R_2 and R_3 may form a ring

together with the quaternary ammonium nitrogen;

R_4 represents

-H,

-CH₃, or

-CO- R_{4-1} , wherein R_{4-1} represents

-(C_1 - C_4 alkyl),

-(C_1 - C_4 alkoxy), or

-NR₄₋₂R₄₋₃, wherein R_{4-2} and R_{4-3}

independently represent -H or -(C_1 - C_4 alkyl);

R_5 , R_6 and R_7 independently represent

-H,

-OCH₃,

-OH,

-CONH₂,

-SO₂NH₂,

-F, -Cl, -Br, -I,

-CF₃, or

-(C_1 - C_4 alkyl), optionally substituted with one

or two

-OH,

- (C₁-C₄ alkoxy),
-COOH, or
-CO-O- (C₁-C₃ alkyl); and

X⁻ represents an anion of a pharmaceutically
5 acceptable acid.

2. A quaternary ammonium compound according to claim
1, wherein the carbon stereocenter is (R).

3. A quaternary ammonium compound according to claim
1, wherein the carbon stereocenter is (S).

10 4. A quaternary ammonium compound according to claim
1, which is a mixture of stereoisomers.

5. A quaternary ammonium compound according to claim
1, wherein at least one of R₁, R₂ and R₃ represents C₁-C₃
alkyl.

15 6. A quaternary ammonium compound according to claim
5, wherein at least one of R₁, R₂ and R₃ represents
isopropyl.

7. A quaternary ammonium compound according to claim
6, wherein at least two of R₁, R₂ and R₃ represents
20 isopropyl.

8. A quaternary ammonium compound according to claim
5, wherein at least one of R₁, R₂ and R₃ represents
methyl.

9. A quaternary ammonium compound according to claim
25 5, wherein at least one of R₁, R₂ and R₃ represents ethyl.

10. A quaternary ammonium compound according to
claim 1, wherein R₁ and R₂ jointly form a ring together
with the quaternary ammonium nitrogen.

11. A quaternary ammonium compound according to
30 claim 10, wherein said ring comprises from 4 to 6 carbon
atoms.

12. A quaternary ammonium compound according to
claim 1, wherein R₄ represents -H, -CH₃, or -CO-R₄₋₁,
wherein R₄₋₁ represents C₁-C₄ alkyl.

35 13. A quaternary ammonium compound according to
claim 12, wherein R₄ represents -H.

14. A quaternary ammonium compound according to claim 1, wherein R_5 represents $-H$, $-Br$, $-Cl$, $-CH_3$, or $-CH_2OH$.

15. A quaternary ammonium compound according to claim 14, wherein R_5 represents $-CH_3$.

16. A quaternary ammonium compound according to claim 1, wherein at least one of R_6 and R_7 represents $-H$.

17. A quaternary ammonium compound according to claim 1, wherein both R_6 and R_7 represent $-H$.

18. A quaternary ammonium compound according to claim 1, wherein X^- is selected from the group consisting of the anions of the following acids: tartaric, hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, citric, methanesulfonic, $CH_3-(CH_2)_n-COOH$ where n is 0 thru 4, $HOOC-(CH_2)_n-COOH$ where n is 1 thru 4, $HOOC-CH=CH-COOH$, and benzoic.

19. A quaternary ammonium compound according to claim 18, wherein X^- is selected from the group consisting of iodide, bromide, and chloride.

20. A quaternary ammonium compound according to claim 19, wherein X^- represents iodide.

21. A quaternary ammonium compound according to claim 19, wherein X^- represents chloride.

22. A quaternary ammonium compound according to claim 19, wherein X^- represents bromide.

23. A quaternary ammonium compound according to claim 1, which is selected from the group consisting of

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,

(3R)-N-ethyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide,

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenyl-N-propylpropan-1-aminium iodide,

- (3R)-N-benzyl-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropan-1-aminium iodide,
(3R)-N-(tert-butyl)-3-(2-hydroxy-5-methylphenyl)-N,N-dimethyl-3-phenylpropan-1-aminium
5 bromide,
(3R)-3-[2-hydroxy-5-(hydroxymethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
(3R)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
10 (3S)-3-(2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
(3R)-3-(5-chloro-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
(3R)-3-(5-bromo-2-hydroxyphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
15 (3R)-3-[2-(acetyloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
(3R)-3-[2-(isobutyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
20 (3R)-3-(4-fluorophenyl)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium bromide,
(3R)-3-[2-hydroxy-5-(trifluoromethyl)phenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium
25 bromide,
(3R)-3-[2-(isobutyryloxy)-5-hydroxymethylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
(3R)-3-{2-(acetyloxy)-5-
30 [(acetyloxy)methyl]phenyl}-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
2-{(1R)-3-[diisopropyl(methyl)ammonio]-1-phenylpropyl}-4-methylbenzenolate,
(3R)-N,N-diisopropyl-3-(2-methoxy-5-
35 methylphenyl)-N-methyl-3-phenylpropan-1-aminium iodide,

- (3R)-3-[2-(butyryloxy)-5-methylphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride,
5 5-hydroxy-N-[(3R)-3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-N-isopropyl-N-methylpentan-1-aminium iodide,
(3R)-3-(2-hydroxy-4-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
10 3,3-bis(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methylpropan-1-aminium iodide,
(3R)-3-[5-(aminocarbonyl)-2-hydroxyphenyl]-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
3,3-bis(2-methoxyphenyl)-N,N-diisopropyl-N-
15 methylpropan-1-aminium iodide,
1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpyrrolidinium iodide,
1-ethyl-1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]pyrrolidinium iodide,
20 1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylpiperidinium iodide, and
1-[3-(2-hydroxy-5-methylphenyl)-3-phenylpropyl]-1-methylazepanium iodide.

24. A quaternary ammonium compound according to
25 claim 23, which is selected from the group consisting of

- (3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium iodide,
(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium bromide,
30 and

(3R)-3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-N-methyl-3-phenylpropan-1-aminium chloride.

25. A pharmaceutical composition comprising a
therapeutically effective amount of a quaternary ammonium
35 compound according to any one of claims 1-24, and a
suitable pharmaceutical carrier therefor.

26. A quaternary ammonium compound according to any one of claims 1-24 for use as a medicament.

27. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a
5 medicament for treating asthma.

28. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating chronic obstructive pulmonary disease (COPD).

10 29. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating rhinorrhea due to the common cold.

15 30. Use of a quaternary ammonium compound according to any one of claims 1-24 for the manufacture of a medicament for treating allergic rhinitis.

31. A method of treating asthma in a mammal, including man, comprising administering to said mammal, in need of such a treatment, a therapeutically effective
20 amount of a quaternary ammonium compound according to any one of claims 1-24.

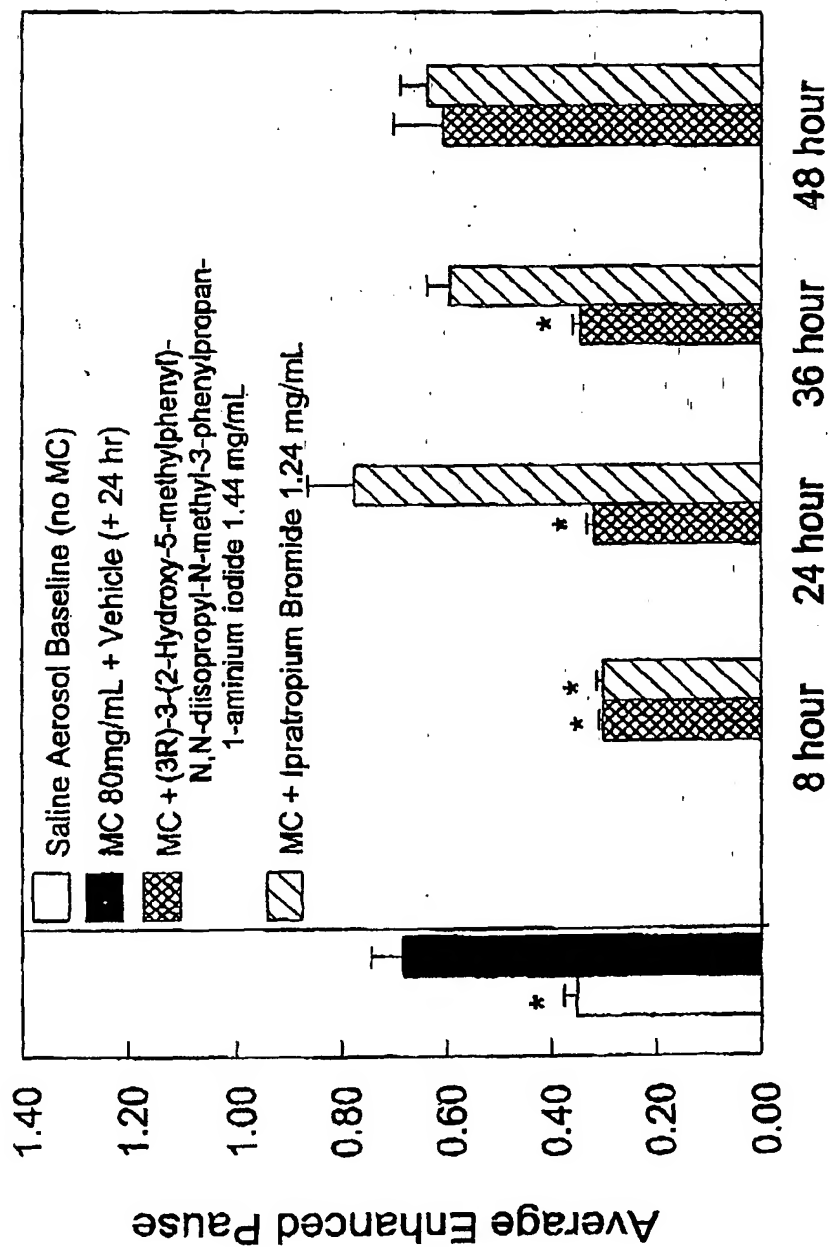
32. A method of treating chronic obstructive pulmonary disease (COPD) in a mammal, including man, comprising administering to said mammal, in need of such
25 a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

33. A method of treating allergic rhinitis in a mammal, including man, comprising administering to said
30 mammal, in need of such a treatment, a therapeutically effective amount of a quaternary ammonium compound according to any one of claims 1-24.

34. A method of treating rhinorrhea due to the common cold in a mammal, including man, comprising
35 administering to said mammal, in need of such a treatment, a therapeutically effective amount of a

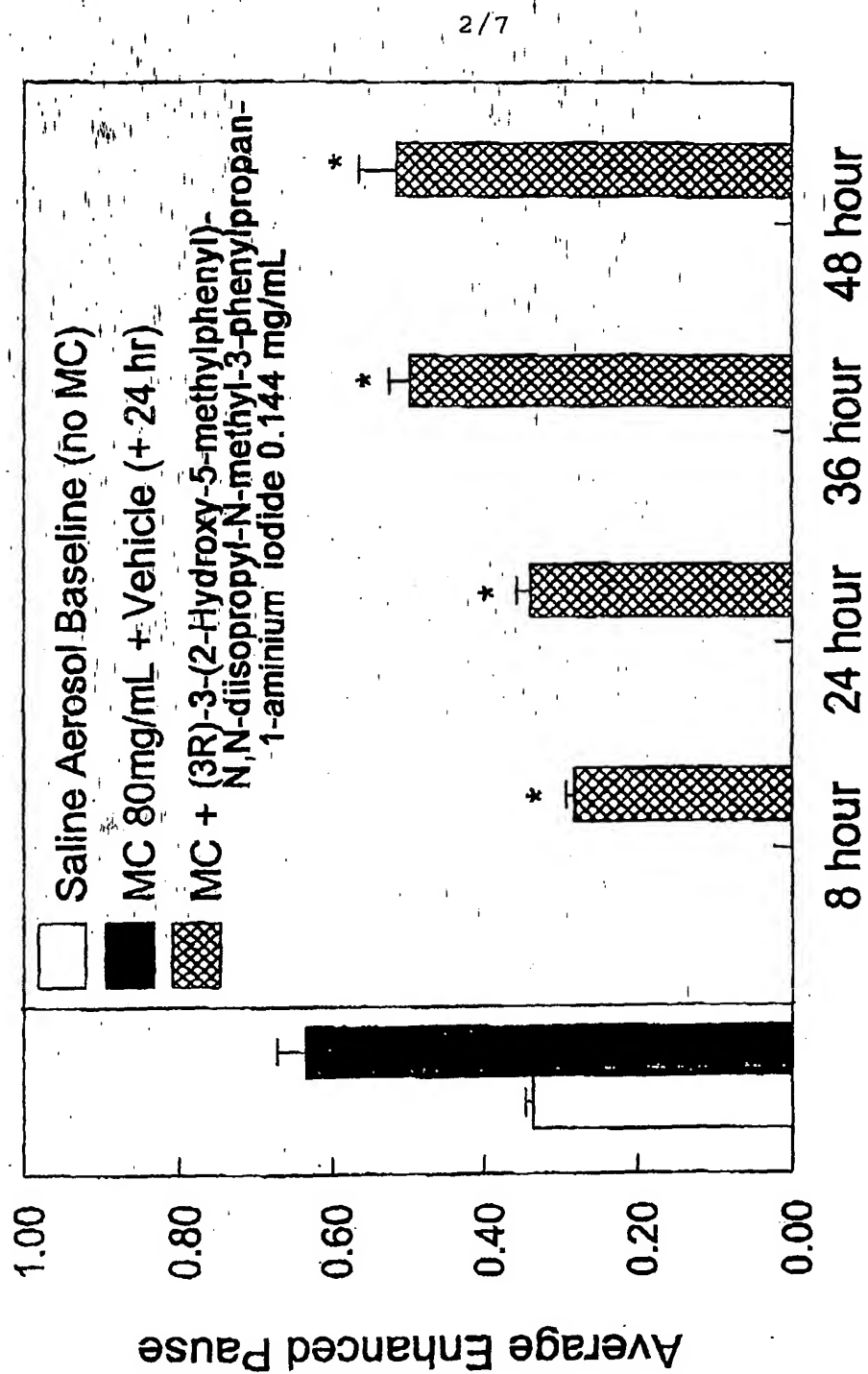
quaternary ammonium compound according to any one of claims 1-24.

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Drawings

*: p < 0.05 between Vehicle/MC and all other groups

FIGURE 1



* : $p < 0.05$ between Vehicle/MC and all other groups

FIGURE 2

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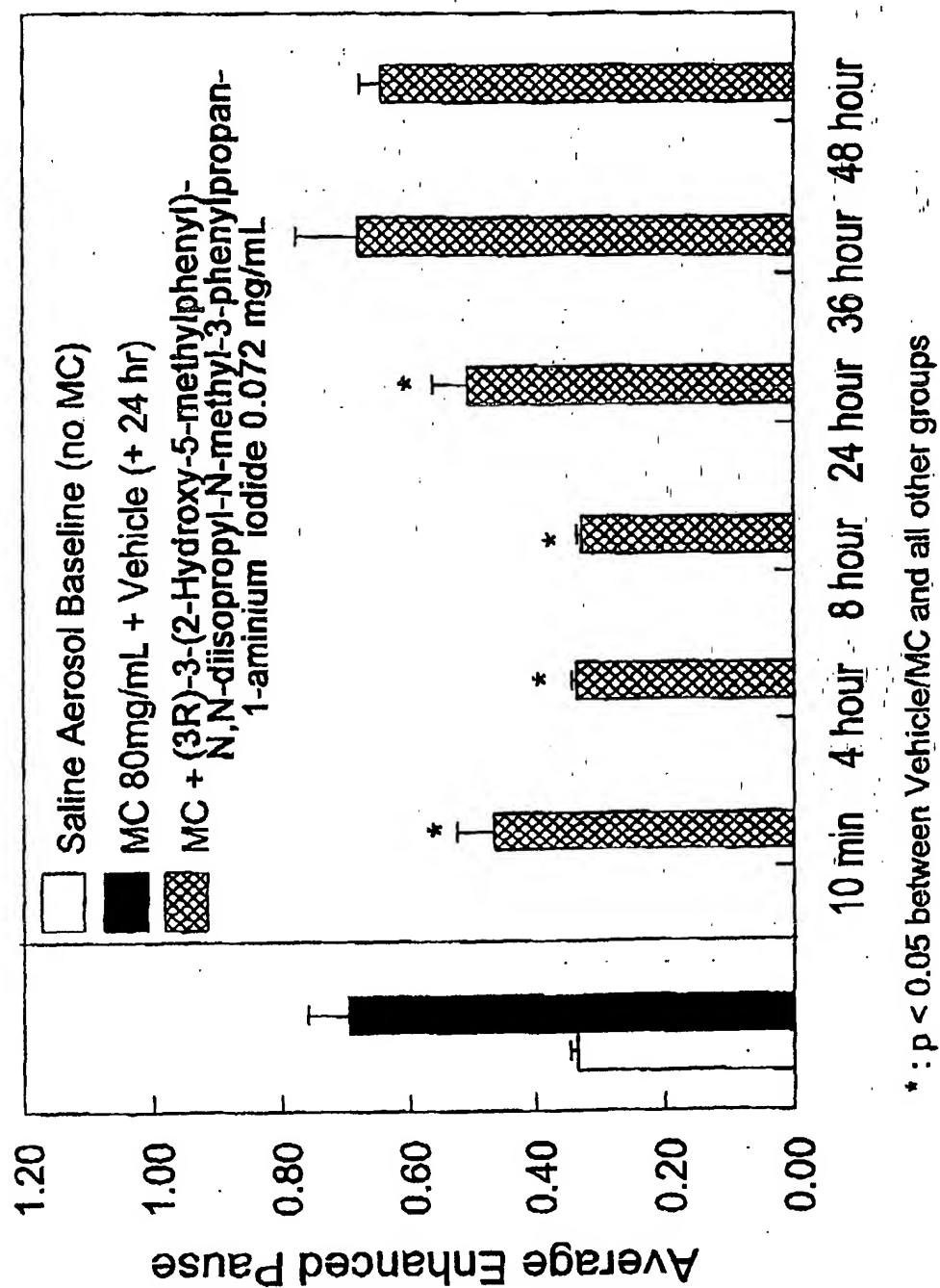
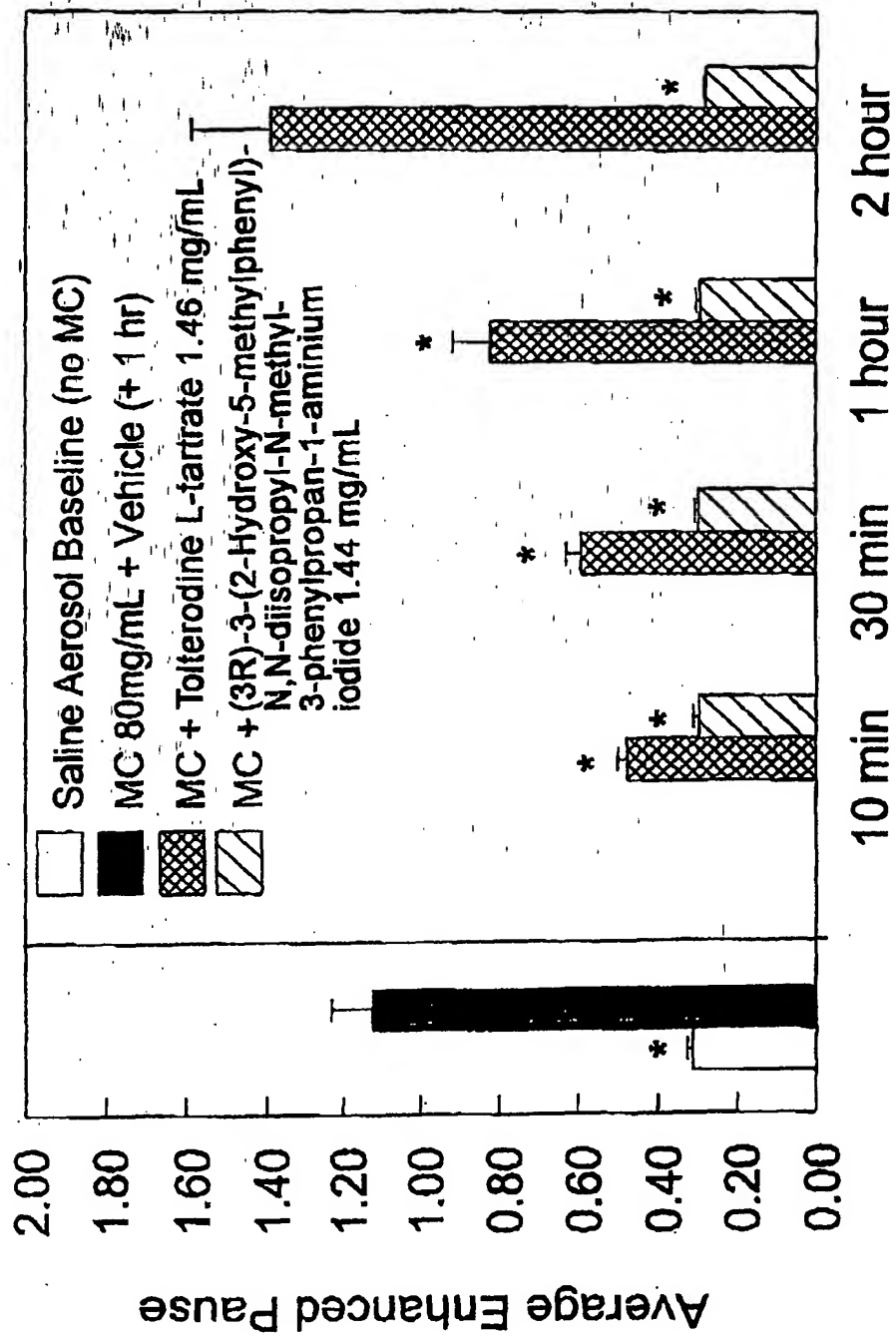


FIGURE 3

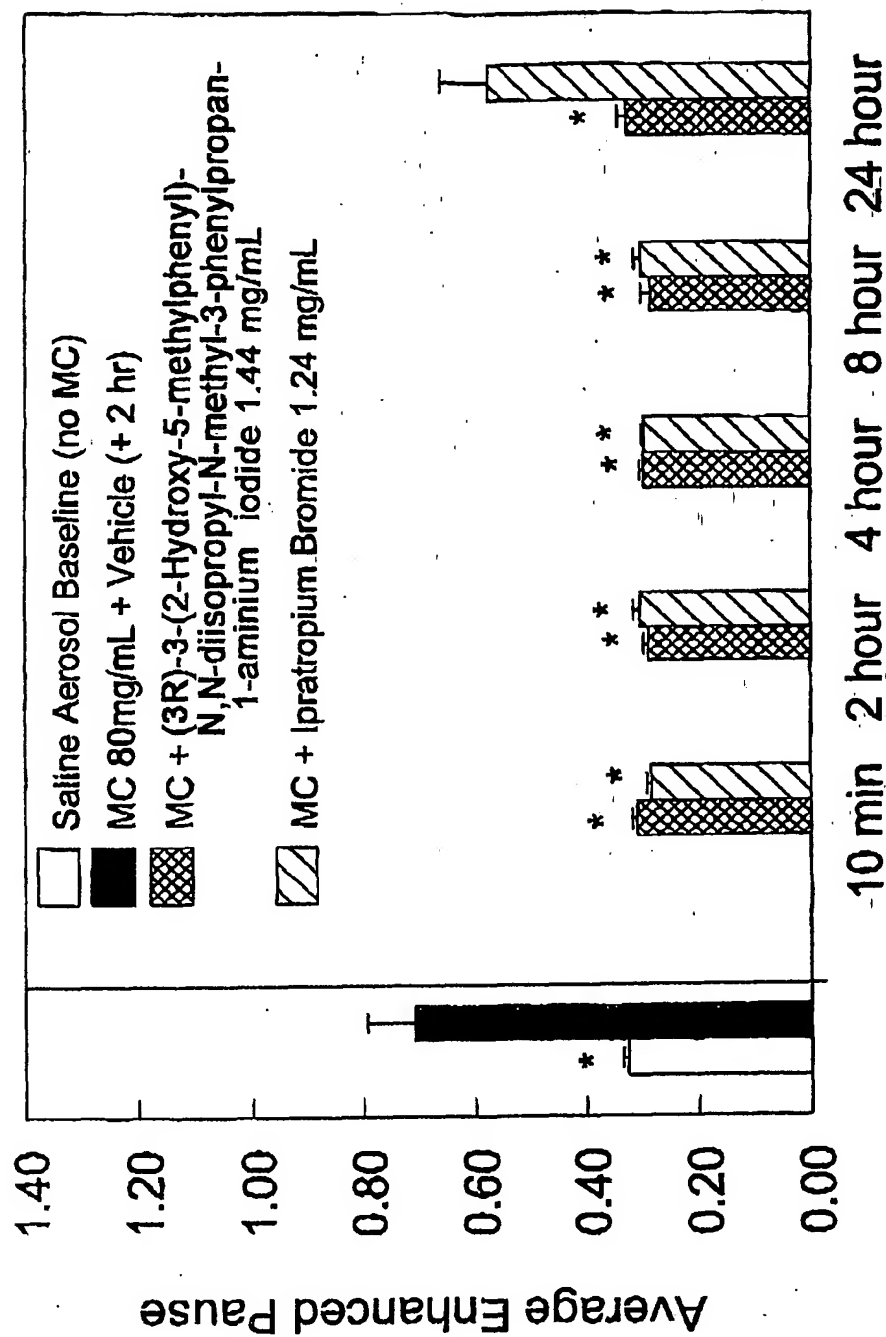
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*: p < 0.05 between Vehicle/MC and all other groups

FIGURE 4

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* : p < 0.05 between Vehicle/MC and all other groups

FIGURE 5

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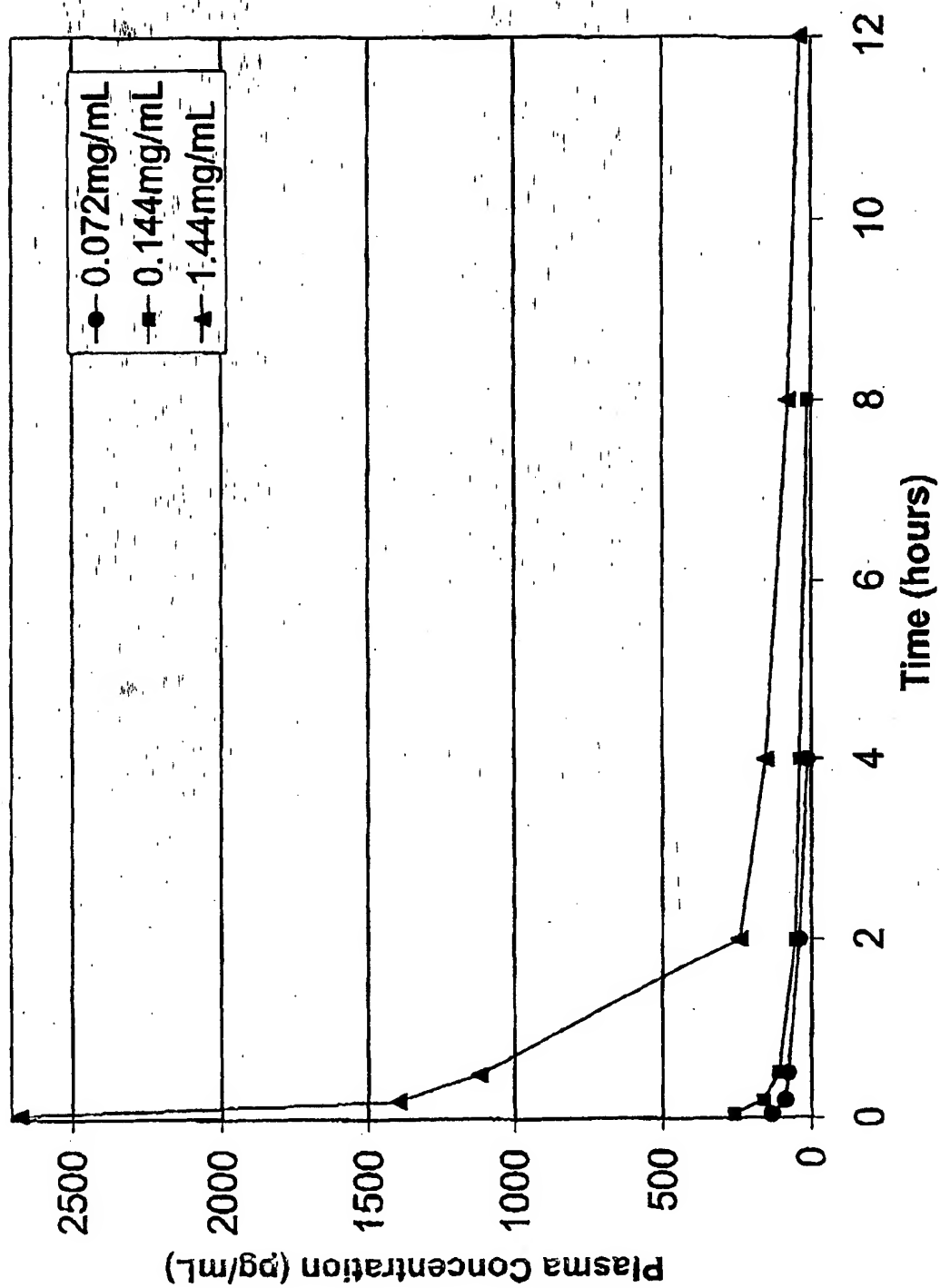


FIGURE 6

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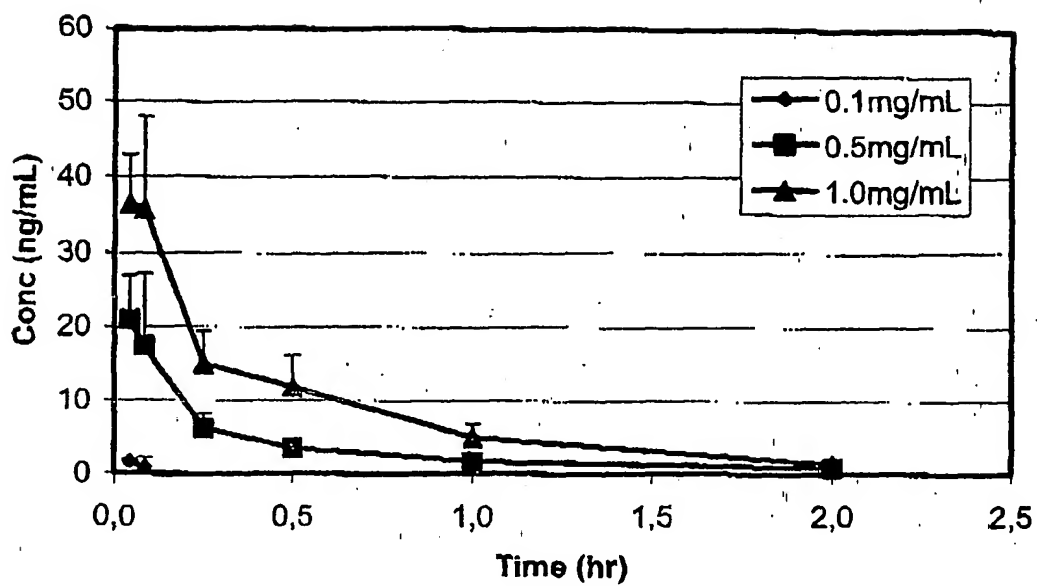


FIGURE 7

INTERNATIONAL SEARCH REPORT

Internu ublication No

PCT/US 02/34529

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C211/27 C07C211/29 C07C215/54 C07C215/66 C07C219/28
 C07D295/02 C07C217/62 A61K31/14 A61K31/452 A61K31/40
 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2 592 191 A (WAYNE RUDDY ARLO) 8 April 1952 (1952-04-08) column 1, line 1 - line 11; claims	1-34
A	US 5 382 600 A (JOENSSON NILS A ET AL) 17 January 1995 (1995-01-17) cited in the application column 31 - column 36; claims; table 1	1-34
A	WEBER R W: "ROLE OF ANTICHOLINERGICS IN ASTHMA" ANNALS OF ALLERGY, AMERICAN COLLEGE OF ALLERGY AND IMMUNOLOGY, US, vol. 65, November 1990 (1990-11), pages 348-360, XP000979858 ISSN: 0003-4738 the whole document	27-34

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

25 March 2003

Date of mailing of the international search report

02/04/2003

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European Patent Office, P.B. 5818 Patentlaan 2
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INTERNATIONAL SEARCH REPORT

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